

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202129Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
		NDA NUMBER	
		202129	
		NAME OF APPLICANT/NDA HOLDER	
		Nycomed GmbH	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME)			
To be determined			
ACTIVE INGREDIENT(S)		STRENGTH(S)	
Pregna-1,4-diene-3,20-dione, 16,17-[[[(R)-cyclohexylmethylene] bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11beta, 16alpha)-		37 micrograms	
DOSAGE FORM			
Aerosol, metered, nasal inhalation			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number		b. Issue Date of Patent	c. Expiration Date of Patent
5,482,934		01/09/1996	10/24/2017
d. Name of Patent Owner		Address (of Patent Owner)	
Nycomed GmbH		Byk-Gulden-Str. 2	
		City/State	
		78467 Konstanz	
		ZIP Code	FAX Number (if available)
		Germany	+49-7531-84-5321
		Telephone Number	E-Mail Address (if available)
		+49-7531-84-0	Dekon.IPPA-DE@nycomed.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
Ryan Walsh Vice President, Intellectual Property Nycomed US Inc.		210 Park Avenue	
		City/State	
		Florham Park, NJ	
		ZIP Code	FAX Number (if available)
		07932	973-236-1433
		Telephone Number	E-Mail Address (if available)
		973-805-4540	ryan.walsh@nycomedus.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		☐ Yes ☐ No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
5, 7	☒ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Indication from proposed labeling: TRADENAME Nasal Aerosol is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. Patent claims: Methods of treating inflammatory conditions.
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification	
6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct. Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) 	Date Signed 08 Feb. 2011
NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(e)(4) and (d)(4).	
Check applicable box and provide information below.	
☐ NDA Applicant/Holder ☐ Patent Owner	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official ☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Dr. Bernd Kratzer c/o Nycomed GmbH	
Address Byk-Gulden-Str. 2	City/State 78467 Konstanz
ZIP Code Germany	Telephone Number +49-7531-84-0
FAX Number (if available) +49-7531-84-5321	E-Mail Address (if available) Dekon.IPPA-DE@nycomed.com
The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer (HFA-710) 5600 Fishers Lane Rockville, MD 20857 <i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i>	

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DOSAGE FORM Aerosol, metered, nasal inhalation			
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		c. Expiration Date of Patent (b) (4)	
d. Name of Patent Owner (b) (4)		Address (of Patent Owner) (b) (4)	
		City/State (b) (4)	
		ZIP Code (b) (4)	FAX Number (if available) (b) (4)
		Telephone Number (b) (4)	E-Mail Address (if available) (b) (4)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Ryan Walsh Vice President, Intellectual Property Nycomed US Inc.		Address (of agent or representative named in 1.e.) 210 Park Avenue City/State Florham Park, NJ ZIP Code 07932 Telephone Number 973-805-4540 FAX Number (if available) 973-236-1433 E-Mail Address (if available) ryan.walsh@nycomedus.com	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
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2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

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2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

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4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) (b) (4)	Date Signed Feb 23, 2011
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Check applicable box and provide information below.	
☐ NDA Applicant/Holder ☐ Patent Owner	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official ☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name (b) (4)	
Address (b) (4)	City/State (b) (4)
ZIP Code (b) (4)	Telephone Number (b) (4)
FAX Number (if available) (b) (4)	E-Mail Address (if available) (b) (4)
The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer (HFA-710) 5600 Fishers Lane Rockville, MD 20857 <i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i>	

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d. Name of Patent Owner (b) (4)		Address (of Patent Owner) (b) (4)	
		City/State (b) (4)	
		ZIP Code (b) (4)	FAX Number (if available) 651-736-3833
		Telephone Number (b) (4)	E-Mail Address (if available) (b) (4)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Ryan Walsh Vice President, Intellectual Property Nycomed US Inc.		Address (of agent or representative named in 1.e.) 210 Park Avenue City/State Florham Park, NJ ZIP Code 07932 Telephone Number 973-805-4540 FAX Number (if available) 973-236-1433 E-Mail Address (if available) ryan.walsh@nycomedus.com	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

(b) (4)

Feb. 23, 2011

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Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

(b) (4)

Address

(b) (4)

City/State

(b) (4)

ZIP Code

(b) (4)

Telephone Number

(b) (4)

FAX Number (if available)

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(b) (4)

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		ZIP Code (b) (4) 0	FAX Number (if available) (b) (4)
		Telephone Number (b) (4)	E-Mail Address (if available) (b) (4)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Ryan Walsh Vice President, Intellectual Property Nycomed US Inc.		Address (of agent or representative named in 1.e.) 210 Park Avenue City/State Florham Park, NJ ZIP Code 07932 Telephone Number 973-805-4540 FAX Number (if available) 973-236-1433 E-Mail Address (if available) ryan.walsh@nycomedus.com	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		☐ Yes ☐ No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

(b) (4)

Feb. 23, 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

(b) (4)

Address

(b) (4)

City/State

(b) (4)

ZIP Code

(b) (4)

Telephone Number

(b) (4)

FAX Number (if available)

(b) (4)

E-Mail Address (if available)

(b) (4)

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use**

NDA NUMBER

202129

NAME OF APPLICANT/NDA HOLDER

Nycomed GmbH

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

To be determined

ACTIVE INGREDIENT(S)

Pregna-1,4-diene-3,20-dione, 16,17-[[[(R)-cyclohexylmethylene]
bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11beta,
16alpha)-

STRENGTH(S)

37 micrograms

DOSAGE FORM

Aerosol, metered, nasal inhalation

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

(b) (4)

b. Issue Date of Patent

(b) (4)

c. Expiration Date of Patent

(b) (4)

d. Name of Patent Owner

(b) (4)

Address (of Patent Owner)

(b) (4)

City/State

(b) (4)

ZIP Code

(b) (4)

FAX Number (if available)

(b) (4)

Telephone Number

(b) (4)

E-Mail Address (if available)

(b) (4)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Ryan Walsh

Vice President, Intellectual Property

Nycomed US Inc.

Address (of agent or representative named in 1.e.)

210 Park Avenue

City/State

Florham Park, NJ

ZIP Code

07932

FAX Number (if available)

973-236-1433

Telephone Number

973-805-4540

E-Mail Address (if available)

ryan.walsh@nycomedus.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

☐ Yes

☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

☐ Yes

☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

(b) (4)

Feb. 23, 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

(b) (4)

Address

(b) (4)

City/State

(b) (4)

ZIP Code

(b) (4)

Telephone Number

(b) (4)

FAX Number (if available)

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(b) (4)

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Rockville, MD 20857

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Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
		NDA NUMBER	
		202129	
		NAME OF APPLICANT/NDA HOLDER	
		Nycomed GmbH	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME)			
To be determined			
ACTIVE INGREDIENT(S)		STRENGTH(S)	
Pregna-1,4-diene-3,20-dione, 16,17-[[[(R)-cyclohexylmethylene] bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11beta, 16alpha)-		37 micrograms	
DOSAGE FORM			
Aerosol, metered, nasal inhalation			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number		b. Issue Date of Patent	
(b) (4)		(b) (4)	
		c. Expiration Date of Patent	
		(b) (4)	
d. Name of Patent Owner		Address (of Patent Owner)	
(b) (4)		(b) (4)	
		City/State	
		(b) (4)	
		ZIP Code	FAX Number (if available)
		(b) (4)	(b) (4)
		Telephone Number	E-Mail Address (if available)
		(b) (4)	(b) (4)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
Ryan Walsh Vice President, Intellectual Property Nycomed US Inc.		210 Park Avenue	
		City/State	
		Florham Park, NJ	
		ZIP Code	FAX Number (if available)
		07932	973-236-1433
		Telephone Number	E-Mail Address (if available)
		973-805-4540	ryan.walsh@nycomedus.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
☐ Yes ☒ No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?			
☐ Yes ☐ No			

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

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6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) (b) (4)

Date Signed

Feb. 23, 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

(b) (4)

Address

(b) (4)

City/State

(b) (4)

ZIP Code

(b) (4)

Telephone Number

(b) (4)

FAX Number (if available)

(b) (4)

E-Mail Address (if available)

(b) (4)

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Food and Drug Administration
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Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
		NDA NUMBER 202129	
		NAME OF APPLICANT/NDA HOLDER Nycomed GmbH	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) To be determined			
ACTIVE INGREDIENT(S) Pregna-1,4-diene-3,20-dione, 16,17-[[[(R)-cyclohexylmethylene] bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11beta, 16alpha)-		STRENGTH(S) 37 micrograms	
DOSAGE FORM Aerosol, metered, nasal inhalation			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number (b) (4)		b. Issue Date of Patent (b) (4)	
		c. Expiration Date of Patent (b) (4)	
d. Name of Patent Owner Nycomed GmbH and (b) (4) (address is provided in Notes)		Address (of Patent Owner) Byk-Gulden-Str. 2 City/State 78467 Konstanz ZIP Code Germany Telephone Number +49-7531-84-0	
		FAX Number (if available) +49-7531-84-5321 E-Mail Address (if available) Dekon.IPPA-DE@nycomed.com	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Ryan Walsh Vice President, Intellectual Property Nycomed US Inc.		Address (of agent or representative named in 1.e.) 210 Park Avenue City/State Florham Park, NJ ZIP Code 07932 Telephone Number 973-805-4540	
		FAX Number (if available) 973-236-1433 E-Mail Address (if available) ryan.walsh@nycomedus.com	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		☐ Yes ☐ No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

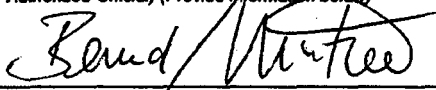
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

08 Feb. 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Dr. Bernd Kratzer c/o Nycomed GmbH

Address

Byk-Gulden-Str. 2

City/State

78467 Konstanz

ZIP Code

Germany

Telephone Number

+49-7531-84-0

FAX Number (if available)

+49-7531-84-5321

E-Mail Address (if available)

Dekon.IPPA-DE@nycomed.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Notes to Form FDA 3542a for U.S. Patent No. (b) (4) for NDA 202129:

Note to Question 1.d: (b) (4) address is:

(b) (4)

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
		NDA NUMBER 202129	
		NAME OF APPLICANT/NDA HOLDER Nycomed GmbH	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) To be determined			
ACTIVE INGREDIENT(S) Pregna-1,4-diene-3,20-dione, 16,17-[[[(R)-cyclohexylmethylene] bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11beta, 16alpha)-		STRENGTH(S) 37 micrograms	
DOSAGE FORM Aerosol, metered, nasal inhalation			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number (b) (4)		b. Issue Date of Patent (b) (4)	
c. Expiration Date of Patent (b) (4)			
d. Name of Patent Owner Nycomed GmbH and (b) (4) (address is provided in Notes)		Address (of Patent Owner) Byk-Gulden-Str. 2 City/State 78467 Konstanz ZIP Code Germany Telephone Number +49-7531-84-0 FAX Number (if available) +49-7531-84-5321 E-Mail Address (if available) Dekon.IPPA-DE@nycomed.com	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Ryan Walsh Vice President, Intellectual Property Nycomed US Inc.		Address (of agent or representative named in 1.e.) 210 Park Avenue City/State Florham Park, NJ ZIP Code 07932 Telephone Number 973-805-4540 FAX Number (if available) 973-236-1433 E-Mail Address (if available) ryan.walsh@nycomedus.com	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		☐ Yes ☐ No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

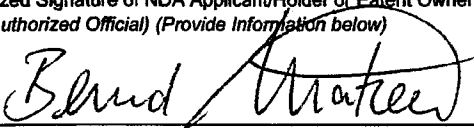
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification	
6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct. Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) 	Date Signed 
NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).	
Check applicable box and provide information below.	
☐ NDA Applicant/Holder ☐ Patent Owner	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official ☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Dr. Bernd Kratzer c/o Nycomed GmbH	
Address Byk-Gulden-Str. 2	City/State 78467 Konstanz
ZIP Code Germany	Telephone Number +49-7531-84-0
FAX Number (if available) +49-7531-84-5321	E-Mail Address (if available) Dekon.IPPA-DE@nycomed.com
The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer (HFA-710) 5600 Fishers Lane Rockville, MD 20857 <i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i>	

Notes to Form FDA 3542a for U.S. Patent No. (b) (4) for NDA 202129:

Note to Question 1.d: (b) (4) address is:

(b) (4)

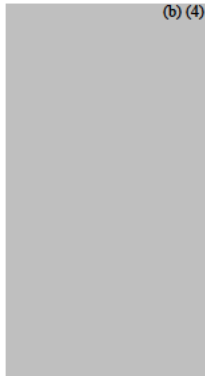
1.3 Administrative Information

1.3.5.2 PATENT CERTIFICATION

Nycomed GmbH hereby certifies that the provisions of 21 U.S.C. 355(b)(2) or (j)(2)(A) do not apply to this application.

Nycomed GmbH hereby certifies the following US Patents claim the Drug Substance (ciclesonide), Drug Product, and/or Methods of Use for which approval is sought in this application.

- 5,482,934



Nycomed GmbH

A handwritten signature in black ink, appearing to read "Bernd Kratzer", is written over a horizontal line.

ppa. Dr. Bernd Kratzer

Vice President Intellectual Property

A handwritten signature in black ink, appearing to read "Olaf Wrobel", is written over a horizontal line.

i. V. Dr. Olaf Wrobel

Senior Patent Counsel

March 02, 2011

Date

1 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

EXCLUSIVITY SUMMARY

NDA # 202129

SUPPL #

HFD #

Trade Name Zetonna Nasal Aerosol

Generic Name ciclesonide nasal aerosol

Applicant Name Nycomed

Approval Date, If Known January 20, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 21658

Alvesco (MDI)

NDA# 22004

Omnaris Nasal Spray

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Study M1-602, 060-622, 060-634, 060-633, and 060-635

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

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

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

Investigation #1 !
IND # 74674 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

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

Investigation #1

YES ☐ NO ☐

Explain:

Investigation #2

!

!

YES ☐

! NO ☐

Explain:

! Explain:

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

YES ☐

NO ☒

If yes, explain:

=====

Name of person completing form: Colette Jackson
Title: Senior Regulatory Health Project Manager
Date: January 20, 2012

Name of Office/Division Director signing form: Badrul A. Chowdhury
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

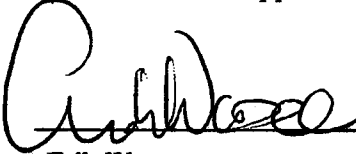
COLETTE C JACKSON
01/20/2012

BADRUL A CHOWDHURY
01/20/2012

1.3. Administrative Information

3. **DEBARMENT CERTIFICATION**

Nycomed GmbH 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.



Erik Worsøe

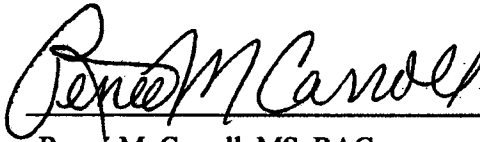
Vice President

Head of International Regulatory Affairs

Nycomed GmbH



Date

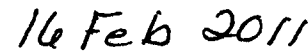


Renee M. Carroll, MS, RAC

US Agent for Nycomed GmbH

Sunovion Pharmaceuticals Inc.

Senior Director, Regulatory Affairs



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202129 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zetonna Established/Proper Name: ciclesonide Dosage Form: nasal aerosol		Applicant: Nycomed Agent for Applicant (if applicable): Sunovion
RPM: Colette Jackson		Division: DPARP
<u>NDA:</u> NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) <u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: <u>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</u>		
❖ Actions		
- Proposed action - User Fee Goal Date is <u>January 21, 2012</u> - Previous actions (<i>specify type and date for each action taken</i>)		☒ AP ☐ TA ☐ CR ☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received

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

❖ Application Characteristics ²		
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ REMS not required Comments:		
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No	
❖ Public communications (<i>approvals only</i>)		
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No	
• Press Office notified of action (by OEP)	☒ Yes ☐ No	
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other	

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

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

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

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

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

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

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	January 20, 2012
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) January 20, 2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 19, 2012
Original applicant-proposed labeling	March 19, 2011
Example of class labeling, if applicable	

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 19, 2012
Original applicant-proposed labeling	March 19, 2011
Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	January 12, 2012
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>) - Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	Proprietary Name Accepted Letter dated January 13, 2012 Proprietary Name Denied Letter dated October 21, 2012 Reviews dated January 12, 2012, and October 21, 2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM July 15, 2011 ☒ DMEPA December 12, 2011 ☒ DRISK DMPP December 19, 2011 ☒ DDMAC December 19, 2011 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing Review dated June 15, 2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC <u>November 30, 2011</u> If PeRC review not necessary, explain: _____ - Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	March 31, June 3, July 11, August 10, September 23, October 4, November 28, and 30, and December 6, 13, and 23(2), 2011 and January 2, 5, 10, 11, 18 and 19, 2012
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg November 3, 2010, and CMC November 22, 2010
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg December 15, 2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Pediatric- October 28, 2011
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None January 20, 2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None December 23, 2012
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 8 dated January 19, 2012
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	CDTL Memo dated December 23, 2011
• Clinical review(s) (<i>indicate date for each review</i>)	May 5, and December 16, 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	MO Review dated December 16, 2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None

⁵ Filing reviews should be filed with the discipline reviews.

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management - REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☐ None requested September 29, 2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None December 19, 2011
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None May 3, and December 21, 2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None May 5, and December 16, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ None
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ None December 7, 2011
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None May 3, and August 4, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None December 28, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None May 5, and December 23, 2011, and January 9, 2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☐ None DBVI Review dated December 6, 2011
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	December 23, 2011
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: April 22, 2011 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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/s/

COLETTE C JACKSON
01/20/2012

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a 6-week double blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. This trial will evaluate the effect of ciclesonide nasal aerosol compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally steady-state PK after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>5/2014</u>
	Study/Trial Completion:	<u>12/2015</u>
	Final Report Submission:	<u>12/2016</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The required study is appropriate as a PMR because a trial evaluating the effect of CIC-HFA on the HPA axis in the ≥ 12 year old population has been completed. This trial demonstrated that CIC-HFA did not have a significant effect on the HPA axis.

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

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The goal of this PMR trial is to evaluate the effect of CIC-HFA on the HPA axis of patients 2-5 years of age with allergic rhinitis. Although a trial in the ≥ 12 year old population has demonstrated no significant effect, the 2-5 year old population may be more susceptible to HPA effects of locally acting nasal corticosteroids.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor is required to conduct a 6 week double-blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with perennial allergic rhinitis 2 to 5 years of age. This trial will evaluate the effect of CIC-HFA compared to placebo on the HPA axis as measured by serum cortisol levels over 6 weeks of treatment. Additionally, the steady state PK profile after 6 weeks of treatment and the relationship to CIC-HFA exposure and change in cortisol exposure will be investigated.

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Required

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

Continuation of Question 4

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

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

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

-
- ☐ Other
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
01/19/2012

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a 2-week double-blind, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 2 to 5 years of age.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2014</u>
	Study/Trial Completion:	<u>12/2015</u>
	Final Report Submission:	<u>05/2016</u>
	Other:	<u></u>

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

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

The required study is appropriate as a PMR because the efficacy and safety of CIC-HFA have already been demonstrated in the ≥ 12 year old population.

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

The goal of this PMR is evaluate the safety and efficacy of CIC-HFA in the 2-5 year old patients with seasonal allergic rhinitis.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor is required to conduct a 2 week double-blind, placebo-controlled efficacy and safety trial with ciclesonide nasal aerosol in patients with seasonal allergic rhinitis patients 2-5 years of age.

Required

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

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Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SALLY M SEYMOUR
01/19/2012

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2014</u>
	Study/Trial Completion:	<u>12/2015</u>
	Final Report Submission:	<u>05/2016</u>
	Other:	

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

The goal of this PMR is evaluate the safety and efficacy of CIC-HFA in the 2-5 year old patients with perennial allergic rhinitis.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor is required to conduct a 12 week double-blind placebo controlled efficacy and safety trial with ciclesonide nasal aerosol in patients with perennial allergic rhinitis 2-5 years of age. The primary efficacy endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SALLY M SEYMOUR
01/19/2012

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-306). The primary endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. The proposed adolescent and adult dose and at least one lower dose will be studied.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	10/2011
	Study/Trial Completion:	12/2012
	Final Report Submission:	12/2013
	Other:	

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

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

The required study is appropriate as a PMR because the efficacy and safety of CIC-HFA have already been demonstrated in the ≥ 12 year old population.

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

The goal of this PMR is to determine the minimum dose at which CIC-HFA is safe and effective in treating 6-11 year old patients with perennial allergic rhinitis.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor is required to conduct a 12 week double-blind, placebo-controlled efficacy and safety trial with ciclesonide nasal aerosol in patients with perennial allergic rhinitis patients 6 to 11 years of age. The primary end point will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. The adolescent and adult dose (74 mcg once daily) and at least one lower dose will be studied.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

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SALLY M SEYMOUR
01/19/2012

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a 2-week double blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 6 to 11 years of age (Study 060-305). The proposed adolescent and adult dose and at least one lower dose will be studied.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	12/2012
	Final Report Submission:	12/2013
	Other:	_____

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

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

The required study is appropriate as a PMR because the efficacy and safety of CIC-HFA have already been demonstrated in the ≥ 12 year old population.

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

The goal of this PMR is to determine the minimum dose at which CIC-HFA is safe and effective in treating 6-11 year old patients with seasonal allergic rhinitis.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor is required to conduct a 2 week double-blind, placebo-controlled efficacy and safety with ciclesonide nasal aerosol in patients with seasonal allergic rhinitis 6-11 years of age (Study 060-305). The proposed adolescent and adult dose and at least one lower dose will be studied..

Required

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

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Continuation of Question 4

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

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

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

-
- ☐ Other
-

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

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

PMR/PMC Development Coordinator:

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

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SALLY M SEYMOUR
01/19/2012

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a 6-week double blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-308). This trial will evaluate the effect of ciclesonide nasal aerosol (74 mcg) compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally the steady-state PK profile after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/2011</u>
	Study/Trial Completion:	<u>06/2012</u>
	Final Report Submission:	<u>12/2013</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The required study is appropriate as a PMR because a trial evaluating the effect of CIC-HFA on the HPA axis in the ≥ 12 year old population has been completed. This trial demonstrated that CIC-HFA did not have a significant effect on the HPA axis.

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

The goal of this PMR trial is to evaluate the effect of CIC-HFA on the HPA axis of patients 6-11 years of age with allergic rhinitis. Although a trial in the ≥ 12 year old population has demonstrated no significant effect, the 6 to 11 year old population may be more susceptible to HPA effects of locally acting nasal corticosteroids.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor is required to conduct a 6 week double-blind HPA axis trial with ciclesonide nasal aerosol in patients with perennial allergic rhinitis 6 to 11 years of age (Study 060-308). This trial will evaluate the effect of ciclesonide nasal aerosol (74 mcg) compared to placebo on the HPA axis as measured by serum cortisol levels over 6 weeks of treatment. Additionally, the steady state PK profile after 6 weeks of treatment and the relationship to CIC-HFA exposure and change in cortisol exposure will be investigated.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SALLY M SEYMOUR
01/19/2012

PMR/PMC Development Template

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

PMR/PMC Description: Improve the product robustness by exploring options to decrease the incidence of separation of canister from actuator and decreasing observed overcounting of the dose counter upon drop testing from a height of 1 meter. Final report submission should include the redesign information and drop testing results with the redesigned drug product, and will be submitted as prescribed in the comparability protocol.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission:	January 2013
	Other:	_____

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

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

While the studies provided show that the actuator and dose counter meet the minimum recommendations for robustness that is acceptable for marketing, a better design will help to prevent separation of the actuator and the canister and can improve the dose counting.

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

During drop testing of the product, the applicant observed that the canister and the actuator separated from each other. In addition in some cases the dose counter miscounted.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor will explore potential solutions to reduce the incidence of separation of the canister from the actuator during drop testing. The sponsor will also explore the feasibility of options available to minimize the frequency of overcounting of the dose counter with drop testing. The sponsor will implement changes in January 2013.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
01/19/2012

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a randomized clinical trial in adolescent (age 12 and older) and adult patients with perennial allergic rhinitis of a minimum of 6 months duration to evaluate the long term safety of Ciclesonide Nasal Aerosol as measured by local nasal and ocular assessments. Include the active comparator OMNARIS Nasal Spray.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>March 2012</u>
	Study/Trial Completion:	<u>June 2013</u>
	Final Report Submission:	<u>December 2013</u>
	Other: <u>NA</u>	<u>MM/DD/YYYY</u>

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

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

The required study is appropriate as a PMR because local nasal toxicity, including perforations, are known to occur with all nasal steroids, and CIC-HFA has demonstrated an acceptable ocular/nasal safety profile for marketing.

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

The goal of this PMR trial is to provide reasonable assurance that the local safety profile of CIC-HFA is similar to Omnaris (an approved nasal steroid with the same active moiety). During CIC-HFA's clinical development program, there were 2 reports of nasal septal perforations, which are rare events seldom observed in pre-marketing trials. Both perforations were noted in the short term exposure data (2-6 weeks), but not in the long term exposure data (6-52 weeks). Additionally, one of the two reports occurred in a patient with a history of significant prior nasal pathology and one perforation may have pre-dated initiation of CIC-HFA. Given increased nasal deposition/retention of CIC-HFA compared to Omnaris, further characterization of local toxicity is required. Evaluation of these events requires nasal examinations that may not be part of routine practice; as such, pharmacovigilance or registry data would be unlikely to report these sentinel events.

With regard to ocular safety, there were no reports of ocular toxicity in the development program; but ocular safety was not directly assessed using ocular examinations as Nycomed had planned to reference ocular safety data from Omnaris. However, in the CIC-HFA development program, it was demonstrated that deposition/retention in the nasal cavity was higher for CIC-HFA compared to Omnaris; therefore, ocular safety data from that program could not be applied to CIC-HFA.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The sponsor is required to conduct a randomized clinical trial in patients with perennial allergic rhinitis. This trial should be a minimum of 6 months in duration, include the active comparator Omnaris, and have a minimum of 300 completers per treatment group. Additionally, the sponsor should allow for a broad patient population including patients with a history of nasal pathology or surgery. Safety assessments should include blinded ocular and nasal examinations.

Required

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

Continuation of Question 4

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

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

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

-
- ☐ Other
-

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

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

PMR/PMC Development Coordinator:

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

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/s/

SALLY M SEYMOUR
01/19/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2012

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230
Subject: NDA 202129 FDA Proposed Labeling	

**Total no. of pages including
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Comments:

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NDA 202129
Ciclesonide Nasal Aerosol

Please refer to your new drug application dated March 21, 2011. We also refer to your January 12, 2012, submission which included revised package insert labeling. We are providing additional FDA recommendations and comments. Our comments and recommendations are not all-inclusive, nor final, and additional comments may be forthcoming as the labeling review continues. We request that you provide your response by 9 am on January 20, 2012.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Enclosure: FDA Proposed Package Insert labeling

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

Drafted: January 10, 2012
Initialed by: Barnes/ January 10, 2012
Michele/ January 10, 2012

Finalized: CCJ/ January 10, 2012

Filename: 202129 January 2012 Label Fax no 3.doc

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/s/

COLETTE C JACKSON
01/19/2012

1.9 Pediatric Administrative Information

1. PEDIATRIC WAIVER REQUEST

Under the Pediatric Research Equity Act (PREA 21 USC 355c), all applications for new dosage forms are required to contain a pediatric assessment unless the applicant has obtained a waiver. Nycomed is requesting a waiver in accordance with the Draft Guidance for Industry (Sept 2005) entitled "How to Comply with the Pediatric Research Equity Act." Table 1 provides the product information specified in the draft guidance.

Table 1: Product Information

Product Name	Ciclesonide Nasal Aerosol
NDA Number	202129
Applicant	Nycomed GmbH
Indication	The proposed indication is for the treatment of symptoms associated with seasonal and perennial allergic rhinitis

1.1. Pediatric Age Group

Nycomed is requesting a waiver of the pediatric study requirements for **ages 0 to less than 2 years**.

1.2. Reason for Waiver

Nycomed is requesting this waiver in pediatric patients aged 0 to less than 2 years because studies would be impossible or impractical.

1.3. Rationale for Waiver

There is a low disease prevalence and significant difficulty in the diagnosis of allergic rhinitis in the 0 to less than 2 years age group. Our waiver proposal with respect to this age group is consistent with the Draft Guidance for Industry (April 2000) entitled Allergic Rhinitis: Clinical Development Programs for Drug Products, that states that based on clinical use experience, the safety of intranasal corticosteroids should be evaluated down to age 2 years. The waiver proposal for this age group is also consistent with the waiver granted by the FDA for OMNARIS® (ciclesonide) Nasal Spray in the October 20, 2006 NDA 22-004 approval letter.

1.4. Certification

Nycomed certifies that the statements made in this request are truthful and accurate.

2. PEDIATRIC DEFERRAL REQUEST

Under the Pediatric Research Equity Act (PREA 21 USC 355c), all applications for new dosage forms are required to contain a pediatric assessment unless the applicant has obtained a deferral. Nycomed is requesting a deferral in accordance with the Draft Guidance for Industry (Sept 2005) entitled "How to Comply with the Pediatric Research Equity Act." Table 1 provides the product information specified in the draft guidance.

Table 1: Product Information

Product Name	Ciclesonide Nasal Aerosol
NDA Number	202129
Applicant	Nycomed GmbH
Indication	The proposed indication is for the treatment of symptoms associated with seasonal and perennial allergic rhinitis

2.1. Pediatric Age Groups

Nycomed requests deferral of the pediatric study requirements in ages 2 to 11 years.

2.2. Reason For Deferral

Ciclesonide nasal aerosol has been studied in adolescents aged 12 years and older. Data will be provided in NDA 202129 for this age group. Pediatric studies were not planned to be initiated until after adolescent and adult studies had been completed and incorporated into a marketing application. The adolescent and adult dose was to be determined based on the results of the pivotal Phase 3 studies.

Additionally, a waiver is being requested for ages 0 to less than 2 years.

2.3. Pediatric Plan

2.3.1. Proposed Studies

Nycomed proposes the following studies to fulfill the pediatric study requirements in ages 2 to 11 years. If efficacy and safety are demonstrated, these studies would be intended to support an indication for allergic rhinitis in this age group.

(b) (4)

1.9 Pediatric Administrative Information

(b) (4)

2.3.2. Rationale

A PK study in children investigating ciclesonide nasal aerosol

(b) (4)

is

proposed.

(b) (4)

(b) (4)

Efficacy is intended to be established

(b) (4)

(b) (4)

2.4. Proposed Deferral Date

A proposed deferral date has yet to be determined.

1/12/12

2. PEDIATRIC DEFERRAL REQUEST

Under the Pediatric Research Equity Act (PREA 21 USC 355c), all applications for new dosage forms are required to contain a pediatric assessment unless the applicant has obtained a deferral. Nycomed is requesting a deferral in accordance with the Draft Guidance for Industry (Sept 2005) entitled "How to Comply with the Pediatric Research Equity Act." Table 1 provides the product information specified in the draft guidance.

Table 1: Product Information

Product Name	Ciclesonide Nasal Aerosol
NDA Number	202129
Applicant	Nycomed GmbH
Indication	The proposed indication is for the treatment of symptoms associated with seasonal and perennial allergic rhinitis

2.1. Pediatric Age Groups

Nycomed requests deferral of the pediatric study requirements in ages 2 to 11 years.

2.2. Reason For Deferral

Ciclesonide nasal aerosol has been studied in adolescents aged 12 years and older. The proposed adolescent and adult dose was determined based on the results of the pivotal Phase 3 studies. Data is provided in NDA 202129 for this age group. Pediatric studies were to be initiated after completion and evaluation of the data from the adolescent and adult studies.

Additionally, a waiver is being requested for ages 0 to less than 2 years.

2.3. Pediatric Plan

2.3.1. Proposed Studies

Nycomed proposes the following studies to fulfill the pediatric study requirements in ages 2 to 11 years. Nycomed proposes to evaluate the safety and efficacy of ciclesonide nasal aerosol in older children (6 to 11 years of age) prior to initiating studies in younger children (2 to 5 years of age). If efficacy and safety are demonstrated, these studies would be intended to support an indication for allergic rhinitis in this age group. The proposed studies in support of an allergic rhinitis indication in children 6 to 11 years of age and to fulfill the PREA requirements are as follows:

- Conduct a 6-week double-blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-308). This trial will evaluate the effect of ciclesonide nasal aerosol (74 mcg) compared to placebo on

1.9 Pediatric Administrative Information

HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally the steady-state PK profile after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated. This protocol was submitted to IND 74,674 on 23 Jun 2011 (Serial #128, Sequence #0071) and enrollment was completed on 03 October 2011. Proposed completion dates are:

- Study initiation: Jul 2011 (completed)
- Study report completion: Jun 2012
- Submission via sNDA: Dec 2013
- Conduct a 2-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 6 to 11 years of age (Study 060-305). The proposed adolescent and adult dose and at least one lower dose will be studied. Proposed completion dates are:
 - Study initiation: Dec 2011
 - Study report completion: Dec 2012
 - Submission via sNDA: Dec 2013
- Conduct a 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-306). The primary endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. The proposed adolescent and adult dose and at least one lower dose will be studied. The protocol was submitted to IND 74,674, (Sequence 0076, Serial Number 133) on 12 October 2011 and the study has been initiated. Proposed completion dates are:
 - Study initiation: Oct 2011 (completed)
 - Study report completion: Dec 2012
 - Submission via sNDA: Dec 2013

Subsequent to the conduct and evaluation of the studies in children 6 to 11 years of age, we propose to support additional PREA requirements and possible indications in children age 2 to 5 years with the following studies. The dose for children age 2 to 5 years will be determined based on the lowest effective dose from the studies in children 6 to 11 years of age.

- Conduct a 2-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 2 to 5 years of age. Proposed completion dates are:
 - Final Protocol Submission: Mar 2014
 - Study report completion: Dec 2015
 - Submission via sNDA: May 2016
- Conduct a 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. The primary

1.9 Pediatric Administrative Information

efficacy endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. Proposed completion dates are:

- Final Protocol Submission: Apr 2014
 - Study report completion: Dec 2015
 - Submission via sNDA: May 2016
- Conduct a 6-week double-blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. This trial will evaluate the effect of ciclesonide nasal aerosol compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally steady-state PK after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated. Proposed completion dates are:
 - Final Protocol Submission: May 2014
 - Study report completion: Dec 2015
 - Submission via sNDA: Dec 2016

2.3.2. Rationale

(b) (4)



1.9 Pediatric Administrative Information

(b) (4)



2.4. Proposed Deferral Date

Proposed deferral dates are presented in Section 2.3.1 Proposed Studies.

1. PROPOSED CLINICAL POST MARKETING REQUIREMENT STUDY

The proposed clinical post marketing requirement study requirement language is as follows:

Conduct a randomized clinical trial in adolescent (age 12 years and older) and adult patients with perennial allergic rhinitis of a minimum of 6 months duration to evaluate the long term safety of ciclesonide nasal aerosol as measured by local nasal and ocular assessments. Include the active comparator OMNARIS (ciclesonide) Nasal Spray.

Final Protocol Submission: March 2012
Trial Completion: June 2013
Final Report Submission: December 2013

2. PROPOSED CHEMISTRY POST MARKETING COMMITMENT

The proposed chemistry post marketing commitment language is as follows:

Improve the product robustness by exploring options to decrease the incidence of separation of canister from actuator and decreasing observed overcounting of the dose counter upon drop testing from a height of 1 meter. Final report submission should include the redesign information and drop testing results with the redesigned drug product, and will be submitted as prescribed in the comparability protocol.

Final Report Submission: January 2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 18, 2012

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 508-357-7491	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 – Ciclesonide Nasal Aerosol

**Total no. of pages including
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Comments:

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NDA 202129
Ciclesonide Nasal Aerosol

We are reviewing your PREA/Deferral Request submitted on January 11, 2012, and your proposed safety PMR language submitted on January 9, 2012. We have alternate proposed PMR language. Provide revised PMR language and dates by 9 am Thursday, January 19, 2012.

Your proposed language in the January 11, 2012, submission:

(b) (4)

FDA proposed language:

Conduct a 6-week double blind HPA axis trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-308). This trial will evaluate the effect of ciclesonide nasal aerosol (74 mcg) compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally the steady-state PK profile after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.

Your proposed language in the January 11, 2012, submission:

(b) (4)

FDA proposed language:

Conduct a 2-week double blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 6 to 11 years of age (Study 060-305). The proposed adolescent and adult dose and at least one lower dose will be studied.

Your proposed language in the January 11, 2012, submission:

(b) (4)

FDA proposed language:

Conduct a 12-week double-blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 6 to 11 years of age (Study 060-306). The primary endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data. The proposed adolescent and adult dose and at least one lower dose will be studied.

Your proposed language in the January 11, 2012, submission:

(b) (4)

FDA proposed language:

Conduct a 2-week double-blind, efficacy and safety trial with ciclesonide nasal aerosol in patients with SAR 2 to 5 years of age.

Your proposed language in the January 11, 2012, submission:

(b) (4)

FDA proposed language:

Conduct a 12-week double blind, placebo-controlled, efficacy and safety trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. The primary efficacy endpoint will be evaluated after 6 weeks of treatment followed by collection of an additional 6 weeks of safety data.

Your proposed language in the January 11, 2012, submission:

(b) (4)

FDA proposed language:

Conduct a 6-week double blind, placebo-controlled HPA axis trial with ciclesonide nasal aerosol in patients with PAR 2 to 5 years of age. This trial will evaluate the effect of ciclesonide nasal aerosol compared to placebo on HPA axis as measured by serum cortisol over 6 weeks of treatment. Additionally

steady-state PK after 6 weeks of treatment and the relationship between study drug exposure and change in cortisol exposure will be investigated.

Your proposed language in the January 9, 2012, submission:



FDA proposed language:

Conduct a randomized clinical trial in adolescent (age 12 and older) and adult patients with perennial allergic rhinitis of a minimum of 6 months duration to evaluate the long term safety of ciclesonide nasal aerosol as measured by local nasal and ocular assessments. Include the active comparator OMNARIS (ciclesonide) Nasal Spray.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: January 17, 2012

Initialed: Barnes/ January 18, 2012
Michele/ January 18, 2012
Seymour/ January 18, 2012

Finalized: CCJ/ January 18, 2012

Filename: 202129 January 2012 PMR PMC fax no 2 FDA proposed.doc

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/s/

COLETTE C JACKSON
01/18/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202129

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, Massachusetts 01752-7010

ATTENTION: Renee Carroll, MS, RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your New Drug Application (NDA) dated March 18, 2011, received March 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ciclesonide Nasal Aerosol, 37 mcg.

We also refer to your December 23, 2011, correspondence, received December 27, 2011, requesting review of your proposed proprietary name, Zetonna. We have completed our review of the proposed proprietary name, Zetonna and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 23, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Colette Jackson, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

CAROL A HOLQUIST
01/13/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 11, 2012

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230
Subject: NDA 202129 FDA Proposed Labeling	

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NDA 202129
Ciclesonide Nasal Aerosol

Please refer to your new drug application dated March 21, 2011. We also refer to your January 3, 2012, submission which included revised carton and container labeling. We are providing additional FDA recommendations and comments. Our comments and recommendations are not all-inclusive, nor final, and additional comments will be forthcoming as the labeling review continues. We request that you provide your response by the close of business on January 13, 2012.

1. The following comments pertain to the Carton labeling:

a. The side panel should be:

Nasal Aerosol contains a solution of ciclesonide in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. The 37 mcg strength of Product™ Nasal Aerosol delivers 37 mcg of ciclesonide from the actuator.

b. The front and back panels should be:

PRODUCT™
(ciclesonide) Nasal Aerosol
37 mcg per actuation
For Intranasal Use Only.
TRADE NAME™ canister should be used with TRADE NAME™ nasal aerosol actuator only.
60 Metered Actuations
Rx Only

c. The bottom panel should be:

PRODUCT™
(ciclesonide) Nasal Aerosol
37 mcg per actuation
60 Metered Actuations

2. The following comment pertains to the canister and actuator labeling:

Improve the legibility of the canister and actuator labels, taking into account as necessary the provisions in 21 CFR 201.10(h)(2).

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Drafted: January 11, 2012
Initialed by: Barnes/ January 11, 2012
Peri/ January 11, 2012
Schroder/ January 11, 2012

Finalized: CCJ/ January 11, 2012

Filename: 202129 January 2012 Label Fax no 4.doc

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/s/

COLETTE C JACKSON
01/11/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 2012

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230
Subject: NDA 202129 FDA Proposed Labeling	

**Total no. of pages including
cover:**

Comments:

Document to be mailed:	YES	xNO
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NDA 202129
Ciclesonide Nasal Aerosol

Please refer to your new drug application dated March 21, 2011. We also refer to your January 3, 2012, submission which included revised package insert, and patient information labeling in response to our December 23, 2011, revised labeling recommendations. We are providing additional FDA recommendations and comments in the attached labeling for the proposed Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive, nor final, and additional comments will be forthcoming as the labeling review continues. We request that you provide your response by the close of business on January 12, 2012.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Enclosure: FDA Proposed Labeling for ciclesonide nasal aerosol

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

Drafted: January 10, 2012
Initialed by: Barnes/ January 10, 2012
Michele/ January 10, 2012

Finalized: CCJ/ January 10, 2012

Filename: 202129 January 2012 Label Fax no 3.doc

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/s/

COLETTE C JACKSON
01/10/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 2012

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 508-357-7491	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 – Ciclesonide Nasal Aerosol

**Total no. of pages including
cover:** 3

Comments:

Document to be mailed: YES xNO

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NDA 202129
Ciclesonide Nasal Aerosol

We are reviewing your PMR protocol synopsis (SEP060-401) submitted on December 30, 2011. Below are our comments regarding the proposed ophthalmologic safety evaluations. Provide a revised protocol synopsis addressing these comments along with proposed language and dates for this PMR and the chemistry PMC by COB Monday, January 9, 2012.

1. The protocol should specify that the ocular examinations will be performed by a physician with training in the use of a slit lamp.
2. Best Corrected Visual acuity should be assessed at each ophthalmic evaluation. Intraocular pressure should be assessed at Visit 1 (Baseline), Visit 5 (Day 90 ± 7), and end of the trial.
3. The protocol should specify a standardized grading system for the evaluation of cataracts (e.g. Lens Opacities Classification System II or III) should it be necessary.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: January 5, 2012

Initialed: Barnes/ January 5, 2012
Lim/ January 5, 2012
Michele/ January 5, 2012

Finalized: CCJ/ January 5, 2012

Filename: 202129 January 2012 PMR PMC fax.doc

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/s/

COLETTE C JACKSON
01/05/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 2, 2012

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 508-357-7491	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 – Ciclesonide Nasal Aerosol

**Total no. of pages including
cover:** 3

Comments:

Document to be mailed: YES xNO

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NDA 202129
Ciclesonide Nasal Aerosol

Your application (NDA 202,129) for ciclesonide HFA is currently under review. We have the following comment.

You have proposed (b) (4) acceptance criteria for APSD testing. Provide drug product data (b) (4) to justify the proposed (b) (4) testing of APSD. Alternately, we recommend that you revise the acceptance criteria to the single tier approach as recommended in the Agency's draft guidance.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: December 29 2011

Initialed: Barnes/ December 29, 2011
Peri/ December 30, 2011

Finalized: CCJ/ January 2, 2012

Filename: 202129 December 2011 CMC fax for CMC Tcon.doc

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/s/

COLETTE C JACKSON
01/02/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2011

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 FDA Proposed Labeling

**Total no. of pages including
cover:**

Comments:

Document to be mailed:	YES	xNO
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NDA 202129
Ciclesonide Nasal Aerosol

Please refer to your new drug application submission dated March 21, 2011. We also refer to your December 20, 2011, submission which included revised package insert and patient package insert in response to our December 13, 2011, revised labeling recommendations. We are providing additional FDA recommendations and comments in the attached labeling for the proposed Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Note that the track changes are based on the FDA-proposed version of the label from December 13, 2011. Our comments and recommendations are not all-inclusive, nor final, and additional comments will be forthcoming as the labeling review continues. We request that you provide your response by the close of business on January 3, 2012.

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.
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)

1. Revise the statement (b) (4)
(b) (4) to read “Usual Dosage: See Prescribing Information.”

2. Delete the statement

(b) (4)

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Enclosure: FDA Proposed Labeling for ciclesonide nasal aerosol

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

Drafted: December 22, 2011
Initialed by: Barnes/ December 23, 2011
Lim/ December 22, 2011
Michele/ December 22, 2011
Pei/ December 22, 2011
Robison/ December 22, 2011
Shaw/ December 22, 2011
Peri/ December 22, 2011
Schroeder/ December 22, 2011
Fan/ December 22, 2011
Doddapaneni/ December 22, 2011
Buenconsejo/ December 22, 2011
Gilbert-McClain/ December 23, 2011

Finalized: CCJ/ December 23, 2011

Filename: 202129 December 2011 Label Fax no 2.doc

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/s/

COLETTE C JACKSON
12/23/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202129

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, Massachusetts 01752-7010

ATTENTION: Renee Carroll, MS, RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your New Drug Application (NDA) dated March 18, 2011, received March 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ciclesonide HFA Nasal Aerosol, 37 mcg.

We acknowledge receipt of your December 7, 2011 correspondence, on December 7, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of December 7, 2011.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nichelle Rashid, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Colette Jackson, (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

CAROL A HOLQUIST
12/23/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2011

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 508-357-7491	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 – Ciclesonide Nasal Aerosol

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 202129
Ciclesonide Nasal Aerosol

Your application (NDA 202,129) for ciclesonide HFA is currently under review. We have the following comment. Please respond by COB January 3, 2012, in order to facilitate our review.

We ask that you conduct the following as a post marketing commitment for ciclesonide nasal aerosol.

Improve the device robustness or redesign the actuator to address the observed separation of actuator from canister and observed overcounting of the dose counter on drop testing from a height of 1 meter. Your final report submission should include the redesign information and drop testing results with the redesigned drug product. Submit the final report per the classification provided in the comparability protocol based on risk (e.g., PAS, CBE 30, CBE, 0).

Include the following required timeline.

Final Report Submission: MM/YY

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: December 23, 2011

Initialed: Barnes/ December 23, 2011
Peri/ December 23, 2011
Seymour/ December 23, 2011

Finalized: CCJ/ December 23, 2011

Filename: 202129 December 2011 CMC fax for PMC.doc

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/s/

COLETTE C JACKSON
12/23/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 13, 2011

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 FDA Proposed Labeling

**Total no. of pages including
cover:**

Comments:

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NDA 202129
Ciclesonide Nasal Aerosol

Please refer to your new drug application submission dated March 21, 2011. We also refer to your July 14, 2011, submission which included revised package insert and patient package insert. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and additional comments will be forthcoming. We request that you provide your response by the close of business on December 19, 2011.

If you have any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager at 301-796-1230.

Enclosure: FDA Proposed Labeling for ciclesonide nasal aerosol

51 Page(s) of Draft Labeling has been Withheld in
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TS)

Drafted: December 9, 2011
Initialed by: Barnes/ December 12, 2011
Michele/ December 13, 2011

Finalized: CCJ/ December 13, 2011

Filename: 202129 December 2011 Label Fax.doc

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/s/

COLETTE C JACKSON
12/13/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Tuesday, December 06, 2011 9:57 AM
To: 'renee.carroll@sunovion.com'
Cc: Jackson, Colette
Subject: Re: Information request for NDA 202129 (Dec. 6-2011)

Dear Ms. Carroll,

We are reviewing the CMC section of your NDA and request following information to continue our evaluation:

In the Comparability Protocol for this NDA, you state that the following parameters will be tested if there is any change in the actuator.



Please cite those sections of the submission that are relevant to the issues under consideration

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

8
b

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/s/

SWATI A PATWARDHAN
12/06/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 30, 2011

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 508-357-7491	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 – Ciclesonide Nasal Aerosol

**Total no. of pages including
cover:** 3

Comments:

Document to be mailed: YES xNO

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NDA 202129
Ciclesonide Nasal Aerosol

Your application (NDA 202,129) for ciclesonide HFA is currently under review. Due to safety concerns regarding nasal toxicity (e.g. erosion, ulceration, septal perforation) and insufficient supportive data regarding ocular toxicity, additional safety data with your product are needed. Due to the increased nasal retention and increased systemic exposure of your product as compared to Omnaris, ocular safety data from the Omnaris development program cannot be used to support your proposed product.

As discussed during the teleconference on November 30, 2011, provide your agreement to conduct the following trial by COB December 9, 2011.

Conduct a randomized clinical trial in patients with perennial allergic rhinitis of minimum 6 months duration to evaluate local and ocular safety with ciclesonide HFA. Include the active comparator, Omnaris. Allow for a broad patient population similar to real-world use, including patients with a history of nasal pathology or nasal surgery. Safety assessments should include blinded nasal and ocular examinations.

Include a trial synopsis and the following required timelines.

Final Protocol Submission: MM/YY
Trial Completion: MM/YY
Final Report Submission: MM/YY

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: November 25, 2011

Initialed: Barnes/ November 25, 2011

Lim/ November 28, 2011

Michele/ November 28, 2011

Seymour/ November 28, 2011

Finalized: CCJ/ November 30, 2011

Filename: 202129 November 2011 MO fax for Nov 30 tcon.doc

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/s/

COLETTE C JACKSON
11/30/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 28, 2011

To: Renee Carroll	From: Colette Jackson
Company: Nycomed c/o Sunovion	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 508-357-7491	Fax number: 301-796-9718
Phone number: 508-357-7598	Phone number: 301-796-1230

Subject: NDA 202129 – Ciclesonide Nasal Aerosol

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 202129
Ciclesonide Nasal Aerosol

Your application for ciclesonide HFA is currently under review. We have the following request for information regarding your application.

Re-code and re-analyze your local adverse events for the 2-6 week exposure period, 6 month exposure period, and 12 month exposure period in the following manner:

- 1) Combine 'instillation site discomfort' with 'nasal discomfort.'
- 2) Combine 'nasal mucosal disorders,' 'nasal septum disorders,' 'nasal ulcer,' and 'nasal septum ulceration' into a single group
 - a. Divide this new combined group into the following subgroups
 - i. Non-ulcerative lesions (e.g. abrasions, excoriations, scabs, irritation)
 1. Irritation
 2. Abrasions/excoriations/scabs
 - ii. Erosions and ulcerations
 1. Erosions
 2. Ulcerations
 - iii. Other

Please provide the requested information by COB Tuesday, December 6, 2011. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: November 25, 2011

Initialed: Barnes/ November 25, 2011
Lim/ November 28, 2011
Michele/ November 28, 2011

Finalized: CCJ/ November 28, 2011

Filename: 202129 MO fax no 2 November 2011.doc

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/s/

COLETTE C JACKSON
11/28/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202129

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, Massachusetts 01752-7010

ATTENTION: Renee Carroll, MS, RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your New Drug Application (NDA) dated March 19, 2011, received March 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ciclesonide Nasal Aerosol, 37 mcg.

We also refer to your July 28, 2011, correspondence, received July 28, 2011, requesting review of your proposed proprietary name (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

1 Page(s) has been Withheld in Full immediately
following this page as B4 (CCI/TS)

We note that you have proposed an alternate proprietary name in your submission dated July 28, 2011. In order to initiate the review of the alternate proprietary name, Omnist, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Colette Jackson at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
10/21/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Tuesday, October 04, 2011 9:46 AM
To: 'renee.carroll@sunovion.com'
Subject: Re: NDA 202-129 Information request 10-4-2011

Dear Ms. Carroll,

We are reviewing your application for NDA 202129 and request following information:
Please refer to your amendment dated July 22, 2011:

- 1) Submit the Population BE analysis for SCU equivalence of V1 and V2 for (b) (4) Nasal Aerosols since the sponsor did not conduct Population BE for SCU equivalence of V1 and V2 for (b) (4) Nasal Aerosols.**
- 2) submit the profile comparison for particle size distribution since the population BE for particle size distribution is not recommended by any FDA guidance. The only reference for profile comparison of particle size distribution is PROFILE ANALYSIS FOR ASSESSING IN VITRO BIOEQUIVALENCE Bin Cheng* and Jun Shao, JOURNAL OF BIOPHARMACEUTICAL STATISTICS, Vol. 12, No. 3, pp. 323–332, 2002**
- 3) Submit both analyses SAS code.**

Please acknowledge the receipt.

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
10/04/2011



NDA 202129

MEETING MINUTES

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Renee M. Carroll, M.S., RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

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

We also refer to the Type C meeting between representatives of your firm and the FDA on September 28, 2011. The purpose of the meeting was to discuss your proposed pediatric development plan.

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

If you have any questions, call me at (301)796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

FDA Meeting Minutes for September 28, 2011, Type C meeting.

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C

Meeting Category: Other

Meeting Date and Time: September 28, 2011 at 2 PM EST

Meeting Location: via teleconference

Application Number: NDA 202129

Product Name: Ciclesonide Nasal Aerosol

Indication: Treatment of SAR and PAR

Sponsor/Applicant Name: Nycomed c/o Sunovion

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Division Director

Meeting Recorder: Colette Jackson
Senior Regulatory Health Project Manager

FDA ATTENDEES:

Center for Drug Evaluation and Research:

Office of Drug Evaluation II, Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Robert Lim, M.D., Clinical Reviewer
Theresa Michele, M.D., Clinical Team Leader
Colette Jackson, Senior Regulatory Health Project Manager

Office of Biostatistics

Joan Buenconsejo, Ph.D., Acting Statistical Team Leader

Office of Clinical Pharmacology

Ying Fan, Ph.D., Clinical Pharmacology Reviewer
Suresh Doddapaneni, Ph.D., Acting Clinical Pharmacology Team Leader

SPONSOR ATTENDEES: Nycomed

Nycomed

Renate Engelstaetter, PhD Medical Director, TA Respiratory Strategy
Sigrid Wienand Senior Group Leader, Regulatory Affairs

Sunovion

Stewart Mueller, MS, MBA, Senior Vice President, Regulatory Affairs and Quality Assurance
Renee Carroll, MS, RAC, Senior Director, Regulatory Affairs
Raymond Claus, MS, Director, Biostatistics
Michael Edwards, Ph.D., Associate Director, Medical Review CRMA
Kathy Grim, Executive Director, CMC Regulatory Affairs
Amy LaForte, Ph.D., Vice President, Regulatory Affairs
Kate Lane, Ph.D., DABT, Director, Toxicology
Paul McGlynn, Ph.D., Executive Director, Program Management
Seth Shapiro, Director, CMC Regulatory Affairs
Robert Tosiello, MS, Executive Director, Biostatistics
Alistair Wheeler, M.D., Vice President, Clinical Affairs and Medical Affairs

1. BACKGROUND

Nycomed sent in a meeting request dated July 18, 2011, to discuss changes in their proposed pediatric development plan. The briefing package was received on September 1, 2011. Upon review of the briefing package, the Division responded to Nycomed's questions via fax on September 23, 2011. The content of that fax is printed below. Nycomed sent their points of clarification document via e-mail on September 27, 2011, to outline their discussion points for the meeting. This document was officially submitted to the NDA on October 5, 2011, and is located in Section 5.0 of these meeting minutes. Any discussion that took place at the meeting is captured directly under the relevant original response in Section 2.0, including any changes in our original position. Nycomed's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2. DISCUSSION

SPONSOR QUESTIONS:

Nonclinical Question

Question 1: Does the Division agree that the nonclinical studies conducted in juvenile and adult animals constitute a complete nonclinical package to support the conduct and clinical studies and expansion of the proposed indication of ciclesonide nasal aerosol to include pediatric subjects 2 – 11 years of age?

FDA Response:

Yes, we agree.

Clinical Questions

Introductory Comment:

We have the following concerns regarding your proposed pediatric program:

- 1. Dose ranging trials are required in the 6-11 year old population. Due to the difficulty with performing patient-reported outcome measured in young children, a dose ranging trial in the 2-5 year old population is unlikely to yield interpretable results. In general, we recommend that the lowest effective dose from dose ranging trials in the 6-11 year old population be applied to the 2-5 year old population.*
- 2. The sample size of the proposed studies is insufficient to provide evidence of local safety. An adequate safety database for this product should be similar in numbers to products with similar indications (i.e. Veramyst, Nasonex). You should note that in neither of those development programs were nasal septum perforations noted. The presence of these events in your program will likely necessitate a larger safety population.*

Question 2: *Does the Division agree with the approach*

(b) (4)

?

FDA Response:

No, we do not.

(b) (4)

Dose ranging trials in the 6-11 year old population will need to take into account these differences in systemic exposure (b) (4)
when selecting the doses to be studied. See introductory comment.

Discussion:

Nycomed stated that they will revise their pediatric plan based upon the FDA comments provided. Nycomed intends to evaluate (b) (4) for their SAR and PAR studies proposed for subjects 6 to 11 years of age. Nycomed asked the FDA if this dose selection is acceptable and if the FDA agrees that no further dose ranging studies are needed. The FDA stated that the dose range was insufficient and strongly encouraged Nycomed to select lower doses. (b) (4)

(b) (4). The PK data, systemic exposure data, and local deposition data all indicate that doses lower than proposed in the sponsor's 6 – 11 year old pediatric study (b) (4) may be effective. The Division asked Nycomed if a lower dose is technically feasible. Nycomed responded (b) (4)

(b) (4)
The FDA stated that an age appropriate formulation and dose must be developed, particularly for use in younger children, and dose ranging must be conducted. If Nycomed conducts the study as proposed, the acceptability of the dose will be a review issue.

Nycomed referred to page 5 of their clarification document which provides Table 2: Allergic Rhinitis Pediatric Safety Populations. Nycomed asked the FDA if the numbers proposed were acceptable. The FDA agreed that it was a reasonable starting point, but larger numbers may be needed.

Nycomed referred to page 7 of their clarification document and asked the FDA if we agree with their proposed statistical strategy. The FDA asked Nycomed to explain (b) (4) testing. Nycomed explained (b) (4)
The FDA stated that there are no objections to this approach, but warned Nycomed that this is risky (b) (4)

Question 3a: *Does the Division agree with the proposed studies and study designs in children 6 to 11 years of age to fulfill PREA requirements and potentially support an indication for the treatment symptoms associated with SAR and/or PAR in this age range?*

FDA Response:

No we do not. See introductory comment. In addition, we recommend that your proposed HPA axis study include a positive control group.

Question 3b: *Does the Division agree with the proposed timeframes for completion and submission of the subsequent study reports (see [Table 1](#)) to fulfill PREA requirements?*

FDA Response:

See introductory comment.

Discussion:

Nycomed referred to FDA response to Question 3a, and asked the FDA if their rationale (b) (4) is acceptable. The FDA stated that we continue to uphold our recommendation. (b) (4)

Question 4a: *Does the Division agree with the sequential approach to development and to the type of studies in pediatric subjects 2 to 5 years of age proposed to fulfill the anticipated PREA commitment to provide safety and efficacy data for and potentially support an indication?*

FDA Response:

No, we do not. While we concur with your plan for sequential development, additional safety data will be required for the 2-5 year old population. See introductory comment. In addition, a HPA axis study will be required in this age range.

Question 4b: *Does the Division agree with the proposed timeframes for completion and submission of the subsequent study reports (see Table 1) to fulfill the PREA requirements?*

FDA Response:

See introductory comment.

Question 5: *Does the Division agree that an indication for ciclesonide nasal aerosol in children 6 to 11 years of age with SAR (b) (4) can be obtained (b) (4)?*

FDA Response:

No, we do not agree. To obtain an indication, adequate safety data must be collected for the target patient population (i.e. 12 week safety data). While there is extensive safety data for Omnaris and Alvesco, the proposed product uses a new delivery device and different dose, both of which may affect local toxicity. See also introductory comment.

Question 6: *Does the Division agree that a (b) (4) could be contemplated to evaluate the safety and efficacy of ciclesonide in subjects 2 to 5 years of age with allergic rhinitis (SAR or PAR)?*

FDA Response:

As this product has not been approved, contemplation of a (b) (4) is premature at this time.

Discussion:

Nycomed asked the FDA if this application will be eligible for a (b) (4) provided that the application is approved. The FDA stated that, in theory, this is possible (b) (4), Nycomed is also assuming that the data in the 6 to 11 year age group will be acceptable. (b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no action items identified during the meeting.

5.0 ATTACHMENTS AND HANDOUTS

September 27, 2011, points of clarification document from Nycomed (officially submitted on October 5, 2011).

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INTRODUCTION

We would like to thank the Division for providing comments to our pediatric development plan meeting questions in such a timely manner. We appreciate the opportunity to discuss the Ciclesonide Nasal Aerosol pediatric development program with the Division at teleconference scheduled for September 28, 2011. We have prepared this document to facilitate the discussion at the teleconference.

Table 1 summarizes the revised overview of the pediatric development program.

We have requested follow up discussion regarding the Division's introductory comments as well as comments to Questions 2, 3, and 4. Additionally, we have provided clarification comments to Question 6.

QUESTION 1: ADEQUACY OF NONCLINICAL PROGRAM

Does the Division agree that the nonclinical studies conducted in juvenile and adult animals constitute a complete nonclinical package to support the conduct and clinical studies and expansion of the proposed indication of ciclesonide nasal aerosol to include pediatric subjects 2 – 11 years of age?

FDA Response:

Yes, we agree.

Sponsor Comment:

No further questions.

Table 1: Overview of Ciclesonide Nasal Aerosol Proposed Pediatric Plan

Study No.	Study Design	Daily Dose	Duration	No. Subjects	Endpoints	Study Target Dates ^a
SEP060-305	Randomized, double-blind, placebo controlled, parallel group safety and efficacy study in children 6 to 11 years of age with SAR	(b) (4)	2 wks	(b) (4)	(b) (4)	Start: Dec 2011 CSR: Dec 2012 sNDA: Dec 2013
SEP060-306	Randomized, double-blind, placebo controlled, parallel group safety and efficacy study in children 6 to 11 years of age with PAR	(b) (4)	12 wks			Start Oct 2011 CSR: Dec 2012 sNDA: Dec 2013
SEP060-308	Randomized, double-blind, placebo controlled, parallel group safety study of HPA axis in children 6 to 11 years of age with PAR	74 mcg	6 wks			Start Jul 2011 CSR: Jun 2012 sNDA: Dec 2013
TBD	Randomized, double-blind, placebo controlled, parallel group safety and efficacy study in children 2 to 5 years of age with SAR	TBD	2 wks			Start Mar 2014 CSR Dec 2015 sNDA: May 2016
TBD	Randomized, double-blind, placebo controlled, parallel group safety and efficacy study in children 2 to 5 years of age with PAR	TBD	12 wks			Start Apr 2014 CSR Dec 2015 sNDA: May 2016
	Randomized, double-blind, placebo controlled, parallel group safety study of HPA axis in children 2 to 5 years of age with PAR	TBD	6 wks			Start May 2014 CSR Dec 2015 sNDA: May 2016

^a Actual dates are bolded.

INTRODUCTORY FDA COMMENTS:

We have the following concerns regarding your proposed pediatric program:

1. Dose ranging trials are required in the 6-11 year old population. Due to the difficulty with performing patient-reported outcome measured in young children, a dose ranging trial in the 2-5 year old population is unlikely to yield interpretable results. In general, we recommend that the lowest effective dose from dose ranging trials in the 6-11 year old population be applied to the 2- 5 year old population.

Sponsor Comment:

Following these comments by the Division, Nycomed agrees to conduct dose-ranging in the Phase 3 SAR and PAR studies in the 6-11 year old population (b) (4)

Please refer to the Sponsor Comments for Question 2 for further detail.

Nycomed also agrees that subject to review of the data from the planned studies in the 6 to 11 year old population, the lowest effective dose identified will be studied in the 2 to 5 year old population.

2. The sample size of the proposed studies is insufficient to provide evidence of local safety. An adequate safety database for this product should be similar in numbers to products with similar indications (i.e. Veramyst, Nasonex). You should note that in neither of those development programs were nasal septum perforations noted. The presence of these events in your program will likely necessitate a larger safety population.

Sponsor Comment:

Nycomed's revised proposal for the SAR and PAR Phase 3 studies (b) (4)

revised proposed database is anticipated to be (b) (4)
(see Table 2).

With respect to the two perforations reported in the adolescent/adult population, we have recently submitted evidence that these events preceded randomization into the clinical trials and are not, therefore treatment emergent adverse events (Sequence 0012 dated September 13, 2011). These two subjects reported nasal perforations at the 2 week visit in two separate SAR studies. Both of these subjects were subsequently shown to have had a history of nasal injury, including nasal perforation, and had not received a decongested nasal examination at their screening visit. For the proposed studies, a detailed review of the subject's medical history, as well as a decongested nasal examination, will be conducted at the screening and baseline visits to ensure that no subjects with a prior history of nasal injury are inadvertently enrolled.

Does the Division agree the expected database as revised is now sufficient?

Table 2: Allergic Rhinitis Pediatric Safety Populations

	Short Term 2-6 wks			Long Term ≥12 wks		
	6-11 years	2-5 years	Total	6-11 years	2-5 years	Total
Ciclesonide Nasal Aerosol	(b) (4)					
OMNARIS	1283	258	1541	790	0	790
VERAMYST	953	271	1224^a	UNK	UNK	372
NASONEX	UNK	UNK	990^b	UNK	UNK	706

Note: Values in this table include placebo and lower than approved doses.

UNK: Unknown.

^a Veramyst values from Summary Basis of Approval; labeling indicates 1,112 total subject exposure short term.

^b Nasonex values do not include placebo.

QUESTION 2: DOSE SELECTION

Does the Division agree with the approach (b) (4)

?

FDA Response:

No, we do not. (b) (4)

Dose ranging trials in the 6- 11 year old population will need to take into account these differences in systemic exposure (b) (4) when selecting the doses to be studied. See introductory comment.

Sponsor Comment:

As noted in response to FDA introductory comment #1, Nycomed agrees to evaluate (b) (4) in the SAR and PAR studies proposed for pediatric subjects 6 to 11 years of age. (b) (4)

(b) (4)

(b) (4)

Given the explanation above, does the Division agree that this approach is adequate to address their comments regarding dose selection and number of subjects in the safety database for studies in children 6 to 11 years of age? If not, could the Division clarify their concern?

With the revised Phase 3 SAR and PAR studies, Nycomed proposes that a

(b) (4)

be conducted.

Does the Division agree with the proposed statistical strategy?

QUESTION 3: PREA PROPOSAL AND DESIGN FOR STUDIES IN CHILDREN 6 TO 11 YEARS OF AGE TO SUPPORT AN INDICATION

Q3a: Does the Division agree with the proposed studies and study designs in children 6 to 11 years of age to fulfill PREA requirements and potentially support an indication for the treatment symptoms associated with SAR and/or PAR in this age range?

FDA Response:

No we do not. See introductory comment. In addition, we recommend that your proposed HPA axis study include a positive control group.

Sponsor Comment:

Please see responses to FDA introductory comment #1 and Question 2 (and Table 1) for the revised pediatric development program.

(b) (4)

Does the Division agree that the design of the ongoing Study 060-308 would be acceptable to fulfill the requirements for HPA axis study in this population?

Q3b: Does the Division agree with the proposed timeframes for completion and submission of the subsequent study reports (see Table 1) to fulfill PREA requirements?

FDA Response:

See introductory comment.

Sponsor Comment:

The revised timeframe for completion of studies, as revised in Question 2 is summarized in Table 1.

Does the Division agree with proposed timeframe for the studies as revised?

QUESTION 4: PREA PROPOSAL AND INDICATION FOR CHILDREN AGE 2 TO 5 YEARS

Q4a: Does the Division agree with the sequential approach to development and to the type of studies in pediatric subjects 2 to 5 years of age proposed to fulfill the anticipated PREA commitment to provide safety and efficacy data for and potentially support an indication?

FDA Response:

No, we do not. While we concur with your plan for sequential development, additional safety data will be required for the 2-5 year old population. See introductory comment. In addition, a HPA axis study will be required in this age range.

Sponsor Comment:

Based on comments from the Division, Nycomed agrees to evaluate in children 2 to 5 years of age placebo and the lowest effective dose identified in the SAR/PAR studies in children 6 to 11 years of age. Nycomed agrees to conduct a separate HPA axis study in children 2 to 5 years of age using the same design considerations utilized in Study 060-308. The overall safety database for this age range will be discussed with the Division following the evaluation of the data obtained in the 6 to 11 year old population.

Q4b: Does the Division agree with the proposed timeframes for completion and submission of the subsequent study reports (see Table 1) to fulfill the PREA requirements?

FDA Response:

See introductory comment.

Sponsor Comment:

The revised timeframe for completion of studies in pediatric patients 2 to 5 years of age, is provided in Table 1.

Does the Division agree with proposed timeframe for the studies as revised?

QUESTION 5: EARLY SAR INDICATION IN CHILDREN AGE 6 TO 11 YEARS

Does the Division agree that an indication for ciclesonide nasal aerosol in children 6 to 11 years of age with SAR (b) (4) can be obtained (b) (4)?

FDA Response:

No, we do not agree. To obtain an indication, adequate safety data must be collected for the target patient population (i.e. 12 week safety data). While there is extensive safety data for OMNARIS and ALVESCO, the proposed product uses a new delivery device and different dose, both of which may affect local toxicity. See also introductory comment.

Sponsor Comment:

No further questions.

QUESTION 6: PROPOSAL (b) (4)

Does the Division agree that a (b) (4) could be contemplated to evaluate the safety and efficacy of ciclesonide in subjects 2 to 5 years of age with allergic rhinitis (SAR or PAR)?

FDA Response:

As this product has not been approved, contemplation of a (b) (4) is premature at this time.

Sponsor Comment:

While we understand that a detailed discussion of a (b) (4) would need to be submitted and evaluated by the Division upon approval of the current NDA under review, we would like guidance from the Division on whether such a program in subjects 2 to 5 years of age with allergic rhinitis (SAR or PAR) would be eligible for consideration of a (b) (4) for ciclesonide.

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/s/

COLETTE C JACKSON
10/28/2011



NDA 202129

MEETING PRELIMINARY COMMENTS

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Renee M. Carroll, M.S., RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

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

We also refer to your July 8, 2011, correspondence received July 8, 2011, requesting a meeting to discuss your pediatric development plan.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 28, 2011, from 2 PM to 3 PM via teleconference between you and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

SPONSOR QUESTIONS:

Nonclinical Question

Question 1: Does the Division agree that the nonclinical studies conducted in juvenile and adult animals constitute a complete nonclinical package to support the conduct and clinical studies and expansion of the proposed indication of ciclesonide nasal aerosol to include pediatric subjects 2 – 11 years of age?

FDA Response:

Yes, we agree.

Clinical Questions

Introductory Comment:

We have the following concerns regarding your proposed pediatric program:

1. Dose ranging trials are required in the 6-11 year old population. Due to the difficulty with performing patient-reported outcome measured in young children, a dose ranging trial in the 2-5 year old population is unlikely to yield interpretable results. In general, we recommend that the lowest effective dose from dose ranging trials in the 6-11 year old population be applied to the 2-5 year old population.
2. The sample size of the proposed studies is insufficient to provide evidence of local safety. An adequate safety database for this product should be similar in numbers to products with similar indications (i.e. Veramyst, Nasonex). You should note that in neither of those development programs were nasal septum perforations noted. The presence of these events in your program will likely necessitate a larger safety population.

Question 2: Does the Division agree with the approach

(b) (4)

?

FDA Response:

No, we do not.

(b) (4)

Dose ranging trials in the 6-11 year old population will need to take into account these differences in systemic exposure (b) (4) when selecting the doses to be studied. See introductory comment.

Question 3a: Does the Division agree with the proposed studies and study designs in children 6 to 11 years of age to fulfill PREA requirements and potentially support an indication for the treatment symptoms associated with SAR and/or PAR in this age range?

FDA Response:

No we do not. See introductory comment. In addition, we recommend that your proposed HPA axis study include a positive control group.

Question 3b: *Does the Division agree with the proposed timeframes for completion and submission of the subsequent study reports (see [Table 1](#)) to fulfill PREA requirements?*

FDA Response:

See introductory comment.

Question 4a: *Does the Division agree with the sequential approach to development and to the type of studies in pediatric subjects 2 to 5 years of age proposed to fulfill the anticipated PREA commitment to provide safety and efficacy data for and potentially support an indication?*

FDA Response:

No, we do not. While we concur with your plan for sequential development, additional safety data will be required for the 2-5 year old population. See introductory comment. In addition, a HPA axis study will be required in this age range.

Question 4b: *Does the Division agree with the proposed timeframes for completion and submission of the subsequent study reports (see [Table 1](#)) to fulfill the PREA requirements?*

FDA Response:

See introductory comment.

Question 5: *Does the Division agree that an indication for ciclesonide nasal aerosol in children 6 to 11 years of age with SAR (b) (4) can be obtained (b) (4)?*

FDA Response:

No, we do not agree. To obtain an indication, adequate safety data must be collected for the target patient population (i.e. 12 week safety data). While there is extensive safety data for Omnaris and Alvesco, the proposed product uses a new delivery device and different dose, both of which may affect local toxicity. See also introductory comment.

Question 6: *Does the Division agree that a (b) (4) could be contemplated to evaluate the safety and efficacy of ciclesonide in subjects 2 to 5 years of age with allergic rhinitis (SAR or PAR)?*

FDA Response:

As this product has not been approved, contemplation of a (b) (4) is premature at this time.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1230

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
09/23/2011



NDA 202129

MEETING REQUEST GRANTED

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Renee M. Carroll, M.S., RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

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

We also refer to your July 8, 2011, correspondence requesting a meeting to discuss your pediatric development plan. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The teleconference is scheduled as follows:

Date: September 28, 2011

Time: 2:00 PM EST

Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the
FDA

CDER Participants (tentative):

Badrul A. Chowdhury, MD, PhD, Division Director
Robert Lim, M.D., Clinical Reviewer
Theresa Michele, M.D., Clinical Team Leader
Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer
Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader
Arthur Shaw, Ph.D., CMC Reviewer
Alan Schroeder, Ph.D., CMC Assessment Lead
Prasad Peri, Ph.D., CMC Branch Chief
Ying Fan, Ph.D., Clinical Pharmacology Reviewer
Suresh Doddapaneni, Ph.D., Acting Clinical Pharmacology Team Leader
Qian Li, Ph.D., Statistical Reviewer
Joan Buenconsejo, Ph.D., Acting Statistical Team Leader

Colette Jackson, Senior Regulatory Health Project Manager

Submit background information for the meeting (three paper copies or one electronic copy to the application and 15 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by August 31, 2011, we may cancel or reschedule the meeting.

Submit the 15 desk copies to the following address:

If sending via USPS, please send to:

Colette Jackson
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 3322
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS
(e.g., UPS, DHL), please send to:

Colette Jackson
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 3322
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

COLETTE C JACKSON
08/10/2011



NDA 202129

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Nycomed GmbH
c/o:
Sunovion Pharmaceuticals Inc.
84 Waterford Drive
Marlborough, Massachusetts 01752-7010

Attention: Renee M. Carroll, MS, RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ciclesonide Nasal Aerosol, 37 mcg.

We acknowledge receipt of your July 8, 2011, correspondence, on July 8, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name [REDACTED] (b) (4). This proposed proprietary name request is considered withdrawn as of July 8, 2011.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nichelle Rashid, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Colette Jackson at 301-796-1230.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
07/18/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, July 11, 2011 5:48 PM
To: 'seth.shapiro@sepracor.com'
Subject: RE: NDA 202129 IR-7-11-2011

Dear Mr. Shapiro,

As per our telephonic conversation this afternoon, we request following information for NDA 202129:

Please provide the data sets to support the comparison between the V1 and V2 actuators. submit the data in SAS format or excel format.

Let me know if you have any questions or concern.

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
07/11/2011



NDA 202129

FILING COMMUNICATION

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Renee M. Carroll, M.S., RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your New Drug Application (NDA) dated March 18, 2011, received March 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ciclesonide Nasal Aerosol.

We also refer to your submissions dated April 11, 13, and 20, 2011.

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

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 20, 2011.

During our filing review of your application, we identified the following potential review issue:

We note that the improvements in ocular symptom score and RQLQ were not consistent in trials 060-622 and 060-634 at the higher ciclesonide dose. Whether or not this discrepancy will affect your proposed labeling claims regarding these outcomes will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Study Report No. 61/2008 contained bioanalytical assay validation data of cortisol in human serum samples from study M1-601. However, a similar report for Study 060-610 could not be found in the NDA. Provide assay validation data of cortisol in human serum samples from Study 060-610. Also, provide the individual serum cortisol AUC analysis dataset. If this information is already submitted, identify the location.
2. Provide original V1.0 protocols and data analysis and reporting plans for studies 060-622, 060-633, and 060-634.

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

3. The following comment pertains to the Highlights Overview section of the product label.
 - a. There should be a white space between each major heading in the Highlights.
4. The following comment pertains to the Table of Contents section of the product label.
 - a. The section headings must be in bold type and should be in upper case letters.
5. The following comment pertains to the Table of Contents and Full Prescribing Information sections of the product label.
 - a. There are no periods after the numbers for the section and subsection headings.
6. The following comment pertains to the Highlights Overview and Full Prescribing Information sections of the product label.
 - a. 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.

We request that you resubmit labeling that addresses these issues by June 24, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 12 to 17 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

BADRUL A CHOWDHURY
06/03/2011



NDA 202129

NDA ACKNOWLEDGMENT

Nycomed GmbH
c/o Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Renee M. Carroll, M.S., RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

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

Name of Drug Product: Ciclesonide Nasal Aerosol

Date of Application: March 18, 2011

Date of Receipt: March 21, 2011

Our Reference Number: NDA 202129

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 20, 2011, in accordance with 21 CFR 314.101(a).

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

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
03/31/2011

**DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATION**
**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

1. APPLICANT'S NAME AND ADDRESS

NYCOMED GMBH
Erik Worsae
Byk-Gulden-Strasse 2
78467 Konstanz
DE

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

202-129

2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE

+49-753184-2599

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

ciclesonide nasal aerosol

6. USER FEE I.D. NUMBER

PD3011091

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? ☐ YES ☒ NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- ☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 738(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Information Management (HFA-710)
1350 Piccard Drive, 4th Floor
Rockville, MD 20850

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Information Management (HFA-710)
1350 Piccard Drive, 4th Floor
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE

TITLE SUP/Vice Head DATE

THORAKS, BENJAMIN RCD Feb 10th 2011

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$1,542,000.00

Form FDA 3397 (01/10)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 74674

MEETING MINUTES

Sunovion Pharmaceuticals Inc.
Attention: Elizabeth George, Ph.D., RAC
Senior Manager, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752-7010

Dear Dr. George:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for **Ciclesonide HFA Nasal Aerosol**.

We also refer to the telecon between representatives of your firm and the FDA on November 22, 2010. The purpose of the meeting was to discuss commercialization of drug product as 60 count canister with V2 actuator.

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

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}
Prasad Peri, Ph.D.
Branch Chief, Branch VIII, Division III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: meeting minutes

Reference ID: 2881173

Reference ID: 3077685



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Nycomed GmbH
Application Number:	IND 74,674
Product Name:	Ciclesonide Nasal Aerosol
Meeting Requestor:	Elizabeth George, Sr. Manager, CMC Regulatory Compliance
Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 22, 2010, 2:30 to 3:30 pm
Meeting Location:	Tele-conference
Received Briefing Package	October 22, 2010
Meeting Chair:	Prasad Peri
Meeting Recorder:	Swati Patwardhan

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment, Division of New Drug Quality Assessment III:

- Eric Duffy, Ph.D., Division Director, DNDQA III
- Prasad Peri, Ph.D., Acting Branch Chief, Branch VIII
- Alan Schroeder, Ph.D., CMC Lead, Branch VIII
- Art Shaw, Ph.D., CMC Reviewer, Branch VIII
- Swati Patwardhan, Regulatory Project Manager

Division of Pulmonary, Allergy, and Rheumatology Products

- Susan Limb, M.D., Team leader
- Pippins Jennifer, M.D., Medical Officer

Reference ID: 2881173

Reference ID: 3077685

Office of Biometrics

- Yi Tsong, Ph.D., Team lead
- Meiyu Shen, Ph.D., Statistician

EXTERNAL ATTENDEES:Sunovion Pharmaceuticals Inc

- Andrea Bauer, Ph.D. Director, Aerosol Development
- Elizabeth George, Ph.D. Senior Manager, Regulatory Affairs
- Paul McGlynn, Ph.D. Executive Program Director
- Kathleen Grim, Executive Director, Regulatory Affairs
- Robert Malone, Director, Development Quality Assurance
- Jagdish Parasrampur, Ph.D., Executive Director, Pharmaceutics
- Seth Shapiro Director, CMC Regulatory Compliance
- Robert Tosiello Executive Director, Biostatistics
- Kenneth Tripp Director Pharmacoeconomics

Nycomed GmbH

- Helgert Mueller, Ph.D., Associate Director, Pharmaceutical CMC Management
- Guenter Stingel, Associate Director, CMC Regulatory Affairs

1.0 BACKGROUND

Ciclesonide HFA Nasal Aerosol is being developed for the treatment of symptoms associated with seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents ≥ 12 years of age and older. A meeting request for a Pre-NDA meeting was submitted on September 16, 2010, to discuss commercialization of drug product as a 60 count canister with a new actuator (V2). The purpose of the meeting was to address various CMC issues related to Module 3 of the planned NDA, and to gain concurrence regarding the questions presented in the briefing package. After receiving preliminary responses on November 19, 2010, the Sponsor requested that the face-to-face meeting be converted to a teleconference. Subsequently, a teleconference was held on November 22, 2010.

2.0 DISCUSSION

- 2.1 Does the Agency agree with the proposed submission strategy for drug substance?

FDA Pre-meeting Response:

Yes, we agree with your submission strategy.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.2 Does the Agency remain in agreement with the plan to rely on ex-valve testing from the Alvesco NDA?

FDA Pre-meeting Response:

Yes, we agree with your plan.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.3 Does the Agency agree with the format and structure for the Define Files and SAS datasets?

FDA Pre-meeting Response:

We do not agree. The following attributes should be included in the test report for the approved Alvesco lots: Lot Number, Unit, Test Date, date of manufacture.

Meeting Discussion:

Prior to the teleconference on November 22, 2010, Sunovion Pharmaceuticals Inc./Nycomed provided comments to Q. 2.3. The meeting discussion was based those comments.

Nycomed Comment:

The Sponsor requests further discussion with the Agency on the requirement for additional fields in the SAS datasets. The data for the canister lots were previously reviewed for the Alvesco NDA and we would like to discuss whether there is some flexibility in the request to gather the historical data that was not present in the original file. Some test attributes will be quite labor intensive to collect. For instance, the Test Date is located only in laboratory notebooks. This will be particularly difficult to retrieve for old lots.

FDA agreed to the sponsor's request for not including test dates in the SAS data sets.

- 2.4 Is the outlined evaluation sufficient to support the evaluation of dose delivery for the V2/60 and V2/30 actuators?

FDA Pre-meeting Response:

You have not specified which method to use for particle size distribution. Please provide the following in the submission:

1. How many replicates will the sponsor obtain for each sampled canister?
2. What is the statistical method for particle size distribution?

Meeting Discussion:

The Sponsor provided following comments prior to the meeting:

Nycomed Comments:

Replicates

Particle size was determined (b) (4)

on a single replicate comprised of five sprays from each canister (once at the beginning and once at the end of canister life).

The total number of (b) (4) tests per actuator version is 60: Ten units from each of the three primary stability batches were paired with 10 actuators from each of the three batches of the V1 actuator. In addition, ten units from each of the three primary stability batches were paired with 10 actuators from each of the three batches of the V2 actuator. Each tested canister was tested at beginning and end of life.

Given this information, is the outlined evaluation described in the briefing package sufficient to support the evaluation of dose delivery for the V2/60 and V2/30 actuators?

Statistical Method

The statistical method to determine comparability of V1 and V2 actuators is outlined on pages 23-24 in the Briefing Package. A portion of the text regarding the method used (b) (4) is reproduced below. We wanted to note there are two typographical errors in the briefing package, which are corrected and presented in ***bold italics***. These typographical errors were not present in the original calculations and did not impact the analyses.

The population equivalence statistical approach utilizes the methodology described in CDER's **Guidance Statistical Approaches to Establishing Bioequivalence** (January 2001) and In Vitro BE Testing (Chow, et. al. 2003). The parameters used for the spray content uniformity and particle size distribution analyses are a scaling standard deviation of 0.10, a variance offset of 0 and the average equivalence limit of 90 to 111%. The scaling standard deviation and the average equivalence limits for both spray content uniformity and particle size distribution (b) (4) are as suggested in the guidance document, for assessing equivalence of in-vitro data. Based on these values, the 95% upper confidence limit for population equivalence criteria are ***1.11*** for spray content uniformity and particle size distribution (b) (4)

A step-by-step description of the methodology for the particle size distribution analysis is as follows:

- Convert particle size distribution data to the natural log scale.
- Set m_T and m_R = number of test and reference samples, respectively.
- Compute the sample mean and standard deviation for the test and reference samples on the natural log scale (μ_T , σ_T , μ_R , σ_R , respectively).
- Set $\delta = \mu_T - \mu_R$

- Set σ_D = maximum of σ_R and 0.10 (the scaling SD). If $\sigma_D = \sigma_R$, then $c = 1$; otherwise $c = 0$
- Set $\zeta = \delta^2 + \sigma_T^2 - \sigma_R^2 - \theta_{BE} \sigma_D^2$ (Chow et al., equation 4), where $\theta_{BE} = 1.11$ (derived from formulas 8-12 in the FDA guidance document, "Statistical Approaches to Establishing Bioequivalence").
- Set $U_{OT} = [\{(m_T - 1) / x\} - 1]^2$, where x is the 5th percentile of the central chi-square distribution with $m_T - 1$ degrees of freedom.
- Set $U_{OR} = [\{(m_R - 1) / x\} - 1]^2$, where x is the 95th percentile of the central chi-square distribution with $m_T - 1$ degrees of freedom.
- Set $U_1 = [(\delta^2 + z\{\sigma_T^2 / m_T + \sigma_R^2 / m_R\}^{0.5})^2 - \delta^2]^2$, where $z = 1.645$, the 95% percentile of the standard normal distribution.
- Set $U_2 = \sigma_T^4 U_{OT}$
- Set $U_3 = (1 + c\theta_{BE})^2 \sigma_R^4 U_{OR}$
- Set $U = U_1 + U_2 + U_3$
- Compute the 95 percent upper confidence bound (UCB):
- $UCB = \delta^2 + \sigma_T^2 - \sigma_R^2 - \theta_{BE} \sigma_D^2 + U^{0.5}$

After reviewing the material, we request that the method be provided to estimate these parameters.

- 2.5 Is the outlined evaluation sufficient to support the evaluation of dose indicator performance for the V2/60 and V2/30 actuators?

FDA Pre-meeting Response:

Yes, we agree.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.6 Does the Agency agree with the approach above to qualify performance of the dose indicator for use with the V2/60 and V2/30 actuators?

FDA Pre-meeting Response:

Yes, we agree.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.7 Is the display and function of the 30 actuation (b)(4) acceptable to the Agency?

FDA Pre-meeting Response:

Yes, it is acceptable. Clarify if the 30 actuation dose counter was used in the clinical trials.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.8 Is the approach to establishing the SCU specification for the V2/30 and V2/60 acceptable?

FDA Pre-meeting Response:

Yes, this approach is acceptable.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.9 Does the Agency agree that the primary stability studies fully support the canisters with the to-be-marketed V2 actuator and that the stability program does not need to be repeated?

FDA Pre-meeting Response:

Yes, we agree.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.10 Is actuator stability proposal acceptable to the Agency?

FDA Pre-meeting Response:

Yes, it is acceptable.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.11 Is the proposal for use of a comparability protocol acceptable to the Agency?

FDA Pre-meeting Response:

Yes, it is acceptable.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

- 2.12 Does Agency agree with the proposal to provide information regarding the implementation of multi-cavity tooling in the annual report?

FDA Pre-meeting Response:

Yes, we agree.

Meeting Discussion:

The sponsor was satisfied with the pre-meeting responses. No discussion occurred during the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 CONCURRENCE:

{See appended electronic signature page}

Prasad Peri
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

5.0 ATTACHMENTS AND HANDOUTS

Attachment received from the applicant dated November 22, 2010

INTRODUCTION

We would like to thank the Division for providing comments to our CMC pre-NDA meeting questions. After reviewing the Agency comments, we would like to change the face to face meeting to a teleconference to address the few remaining questions.

To facilitate this discussion we have prepared the summary located below.

QUESTION 2.1: STRUCTURE OF THE PROPOSED FILING

Does the Agency agree with the proposed submission strategy for Drug Substance?

FDA Response:

Yes, we agree with your submission strategy.

Nycomed Comment:

No further questions.

QUESTION 2.2: CANISTER STABILITY AND CHARACTERIZATION

Does the Agency remain in agreement with the plan to rely on ex-valve testing from the Alvesco NDA?

FDA Response:

Yes, we agree with your plan.

Nycomed Comment:

No further questions.

QUESTION 2.3: FORMAT AND STRUCTURE OF SAS DATA SETS

Does the Agency agree with the format and structure for the Define Files and SAS datasets?

FDA Response:

We do not agree. The following attributes should be included in the test report for the approved Alvesco lots: Lot Number, Unit, Test Date, Date of Manufacture.

Nycomed Comment:

The Sponsor requests further discussion with the Agency on the requirement for additional fields in the SAS datasets. The data for the canister lots were previously reviewed for the Alvesco NDA and we would like to discuss whether there is some flexibility in the request to

gather the historical data that was not present in the original file. Some test attributes will be quite labor intensive to collect. For instance, the Test Date is located only in laboratory notebooks. This will be particularly difficult to retrieve for old lots.

QUESTION 2.4: ACTUATOR DEVELOPMENT AND ASSESSMENT – COMPARISON OF V1 AND V2 ACTUATORS

Is the outlined evaluation sufficient to support the evaluation of dose delivery for the V2/60 and V2/30 actuators?

FDA Response:

You have not specified which method to use for particle size distribution. Please provide the following in the submission:

1. How many replicates will the sponsor obtain for each sampled canister?
2. What is the statistical method for particle size distribution?

Nycomed Comments:

Replicates

Particle size was determined (b) (4) on a single replicate comprised of five sprays from each canister (once at the beginning and once at the end of canister life).

The total number of (b) (4) tests per actuator version is 60: Ten units from each of the three primary stability batches were paired with 10 actuators from each of the three batches of the V1 actuator. In addition, ten units from each of the three primary stability batches were paired with 10 actuators from each of the three batches of the V2 actuator. Each tested canister was tested at beginning and end of life.

Given this information, is the outlined evaluation described in the briefing package sufficient to support the evaluation of dose delivery for the V2/60 and V2/30 actuators?

Statistical Method

The statistical method to determine comparability of V1 and V2 actuators is outlined on pages 23-24 in the Briefing Package. A portion of the text regarding the method used (b) (4) is reproduced below. We wanted to note there are two typographical errors in the briefing package, which are corrected and presented in ***bold italics***. These typographical errors were not present in the original calculations and did not impact the analyses.

The population equivalence statistical approach utilizes the methodology described in CDER's ***Guidance Statistical Approaches to Establishing Bioequivalence*** (January 2001) and In Vitro BE Testing (Chow, et. al. 2003). The parameters used for the spray content uniformity and particle size distribution analyses are a scaling standard deviation of 0.10, a variance offset of 0 and the average equivalence limit of 90 to 111%. The scaling standard deviation and the average equivalence limits for both spray content uniformity

and particle size distribution (b) (4)

are as suggested in the guidance document, for assessing equivalence of in-vitro data. Based on these values, the 95% upper confidence limit for population equivalence criteria are ~~1.11~~ for spray content uniformity and particle size distribution

(b) (4)

A step-by-step description of the methodology for the particle size distribution analysis is as follows:

- Convert particle size distribution data to the natural log scale.
- Set m_T and m_R = number of test and reference samples, respectively.
- Compute the sample mean and standard deviation for the test and reference samples on the natural log scale (μ_T , σ_T , μ_R , σ_R , respectively).
- Set $\delta = \mu_T - \mu_R$
- Set σ_D = maximum of σ_R and 0.10 (the scaling SD). If $\sigma_D = \sigma_R$, then $c = 1$; otherwise $c = 0$
- Set $\zeta = \delta^2 + \sigma_T^2 - \sigma_R^2 - \theta_{BE} \sigma_D^2$ (Chow et al., equation 4), where $\theta_{BE} = 1.11$ (derived from formulas 8-12 in the FDA guidance document, "Statistical Approaches to Establishing Bioequivalence").
- Set $U_{0T} = [\{(m_T - 1) / x\} - 1]^2$, where x is the ~~5%~~ percentile of the central chi-square distribution with $m_T - 1$ **degrees of freedom**.
- Set $U_{0R} = [\{(m_R - 1) / x\} - 1]^2$, where x is the 95th percentile of the central chi-square distribution with $m_T - 1$ **degrees of freedom**.
- Set $U_1 = [(\delta + z\{\sigma_T^2 / m_T + \sigma_R^2 / m_R\}^{0.5})^2 - \delta^2]^2$, where $z = 1.645$, the 95% percentile of the standard normal distribution.
- Set $U_2 = \sigma_T^4 U_{0T}$
- Set $U_3 = (1 + c\theta_{BE})^2 \sigma_R^4 U_{0R}$
- Set $U = U_1 + U_2 + U_3$
- Compute the 95 percent upper confidence bound (UCB):
- $UCB = \delta^2 + \sigma_T^2 - \sigma_R^2 - \theta_{BE} \sigma_D^2 + U^{0.5}$

**QUESTION 2.5: ACTUATOR DEVELOPMENT AND ASSESSMENT –
CHANGES FROM V2/ (b) (4) TO V2/60 AND V2/30**

Is the outlined evaluation sufficient to support the evaluation of dose indicator performance for the V2/60 and V2/30 actuators?

FDA Response:

Yes we agree

Nycomed Comment:

No further questions

QUESTION 2.6: STUDIES TO EVALUATE DOSE INDICATOR

Does the Agency agree with approach above to qualify performance of the dose indicator for use with the V2/60 and V2/30 actuators?

FDA Response:

Yes we agree.

Nycomed Comment:

No further questions.

QUESTION 2.7: 30 ACTUATION DOSE INDICATOR DISPLAY

Is the display and function of the 30 actuation (b) (4) acceptable to the Agency?

FDA Response:

Yes, it is acceptable. Clarify if the 30 actuation dose counter was used in the clinical trials.

Nycomed Comment:

The 30 actuation dose indicator was not used in the clinical trials.

**QUESTION 2.8: SPECIFICATION SETTING FOR SCU AND THE
APPLICABILITY OF THE V1 PRIMARY STABILITY**

Is the approach to establishing the SCU specification for the V2/30 and V2/60 acceptable?

FDA Response:

Yes, this approach is acceptable.

Nycomed Comment:

No further questions.

QUESTION 2.9: APPLICABILITY OF THE V1 PRIMARY STABILITY

Does the Agency agree that the primary stability studies fully support the canisters with the to-be marketed V2 actuator and that the stability program does not need to be repeated?

FDA Response:

Yes, we agree.

Nycomed Comment:

No further questions.

QUESTION 2.10: STABILITY STUDY APPROACH

Is the Actuator stability protocol acceptable to the Agency?

FDA Response:

Yes, it is acceptable.

Nycomed Comment:

No further questions.

QUESTION 2.11: PLAN FOR EVALUATION OF FUTURE ACTUATOR CHANGES – USE OF A COMPARABILITY PROTOCOL

Is the proposal for use of a comparability protocol acceptable to the Agency?

FDA Response:

Yes, it is acceptable.

Nycomed Comment:

No further questions.

QUESTION 2.12: SINGLE CAVITY MOLDS

Does Agency agree with the proposal to provide information regarding the implementation of multi-cavity tooling in the annual report?

FDA Response:

Yes, we agree.

Nycomed Comment:

No further questions.

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/s/

PRASAD PERI
12/21/2010

Reference ID: 2881173

Reference ID: 3077685



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: November 3, 2010, 1:30-2:30 PM
Meeting Location: WO22, Conference Room 1419
Application Number: IND 74,674
Product Name: Ciclesonide HFA Aerosol
Received Briefing Package October 1, 2010
Sponsor Name: Sunovion Pharmaceuticals
Meeting Requestor: Renee Carroll
Director, Regulatory Affairs
Meeting Chair: Badrul A. Chowdhury, MD, PhD
Division Director
Meeting Recorder: Colette Jackson
Senior Regulatory Health Project Manager
Meeting Attendees:

FDA Attendees

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1.0 BACKGROUND

Sunovion (formerly Sepracor, Inc.) submitted a Type B meeting request dated August 26, 2010, to discuss their upcoming NDA. Sunovion's briefing package was submitted on October 1, 2010. Upon review of the briefing package, the FDA responded to Sunovion's questions via fax dated October 29, 2010. The content of the fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response under Section 2.0, including any changes in our original position. Sunovion's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font. Sunovion sent a clarifying document via e-mail on November 1, 2010, to facilitate

discussion at the meeting. Sunovion officially submitted the clarifying document on November 5, 2010, and is included in Section 5.0 Attachments and Handouts.

2.0 DISCUSSION

5.2. Nonclinical Question

Question 1: Adequacy of Nonclinical Program and Plans to /Cross-reference

Extensive nonclinical pharmacology, pharmacokinetic, and toxicology studies have been conducted to support the clinical use of ciclesonide following both oral inhalation and intranasal administration. Details of these studies were included in NDA 22-004 (Omnaris Nasal Spray), approved 20 October 2006 and NDA 21-658 (ALVESCO Inhalation Aerosol), approved 10 January 2008. A comprehensive list of all nonclinical studies completed with ciclesonide is provided in Appendix C. The nonclinical program supporting this ciclesonide application includes: in vitro and in vivo pharmacology, pharmacokinetics and drug metabolism, repeated-dose toxicology studies of up to 6 or 12 months duration in rats and dogs, respectively, in vitro and in vivo genotoxicity testing, carcinogenicity studies in mice and rats, reproductive toxicity studies in rats and rabbits, and safety pharmacology studies.

The design of the nonclinical testing program was based on the ICH Guidelines for the development of pharmaceutical compounds. All pivotal safety studies were GLP compliant; the GLP status of each study is indicated in Appendix C.

Study reports for 186 of the completed nonclinical studies were included in NDA 22-004 (Omnaris®); and 8 studies were submitted in NDA 21-658 (Alvesco). Appendix C notes the location of each report within the specific submissions. In addition to those reports included in previous NDA submissions, 8 new study reports (five DMPK [93/2005, 140/2007, 141/2007, 401/2007, 493/2007] and three toxicology studies [19/2007, 26/2008, 128/2008]) will be included in the Ciclesonide Nasal Aerosol NDA submission (NDA 202129). The results of these additional studies will be summarized in 2.6.4 Pharmacokinetics Written Summary, Section 2.1 Validation of a HPLC-MS/MS Method for the Determination of Ciclesonide and its Metabolite RMI in Dog Serum and 2.6.6 Toxicokinetics Written Summary, Section 6.1 Dose Range-Finding Inhalation Toxicity Study in Juvenile Rats.

Nycomed proposes the following approach for the nonclinical sections of Ciclesonide Nasal

Aerosol NDA 202129:

- Module 2.4, Nonclinical Overview, will be comprised of an in-depth summary of the nonclinical pharmacology, drug metabolism/pharmacokinetics, and safety of studies conducted with ciclesonide, including those previously submitted in the Omnaris and Alvesco NDAs.*
- A tabular listing (Appendix C) of all nonclinical ciclesonide studies and their submission locations (previous NDA location or current NDA location) will also be included in Module 2.4 to facilitate review and cross-reference.*

• **Module 2.6, Nonclinical Written and Tabulated Summaries**, will include the complete tabulated and written summaries for the 8 new studies and will cross-reference the written and tabulated summaries for the previously submitted studies (182 studies from NDA 22-004 Omnaris Nasal Spray and 8 studies from NDA 21-658 Alvesco Inhalation Aerosol).

• **Module 4, Nonclinical Study Reports**, will include only the 8 new nonclinical reports. We propose that nonclinical study reports that were submitted in NDA 22-004 and/or NDA 21-658 need not be resubmitted.

A table providing a list of nonclinical studies and their location (or cross reference location) is provided in Appendix C.

Does the Division agree with our proposed approach for submission and cross-reference of nonclinical studies, and that the studies to be summarized (and cross-referenced) in Module 2 along with the new reports to be included in Module 4 constitute a complete nonclinical package for filing the planned Ciclesonide Nasal Aerosol NDA?

FDA Response:

Your proposed approach for submission and cross reference of nonclinical studies seems reasonable and constitutes a complete nonclinical package for filing the Ciclesonide Nasal Aerosol NDA.

Additional Non-Clinical Comment:

For your NDA submission, provide structures of impurities and intermediates of the drug substance and drug product. Monitor impurities and degradation products of all active ingredients. Refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R)] and degradants in drug products [ICH Q3B(R)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants. Impurities or intermediates that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008) for assessment of impurities to support clinical studies for an IND and NDA.

5.3. Clinical Questions

5.3.1. Efficacy

Question 2: Dose for Commercialization

At the End of Phase 2 meeting on 15 December 2008, the Division agreed that based on results from the dose ranging SAR Study M1-602, ciclesonide once daily doses of 80 mcg and 160 mcg were reasonable to study in the pivotal trials. These doses were studied in all three pivotal efficacy studies (Studies 060-622, 060-634, and 060-633).

The 160 mcg dose as well as a 320 mcg dose were studied in the HPA axis study (Study 060-610). The ongoing scintigraphy study (Study 060-101) is evaluating a single 160 mcg dose (see Appendix F for the protocol synopsis). Finally, the 160 mcg dose is being evaluated in the ongoing long term safety study (Study 060-635). Therefore, across the clinical studies in the ciclesonide nasal aerosol development program, the clinical database includes study data on single and multiple doses ranging from 80 mcg to 320 mcg.

Nycomed and Sepracor have fully evaluated these data and have concluded that the 80 mcg dose is most appropriate for potential commercialization, as it has consistently demonstrated efficacy in both SAR and PAR subjects and presents a good risk-benefit profile. In our view, the 160 mcg dose in both SAR and PAR studies does not demonstrate a sufficiently meaningful incremental benefit over the 80 mcg dose.

Does the Division agree that the 80 mcg dose is the appropriate recommended dose on which the proposed label should be based?

FDA Response:

Yes, we agree, pending review of the data. We note that the summary information provided indicates that no clear dose response was observed, which will be a review issue.

Discussion:

Sunovion stated that they intend to provide dose justification in the ISE and asked the FDA if this is acceptable. The FDA replied that Sunovion should submit any information they deem necessary to support the dose. The comment was intended to express a general concern.

Question 3: Scope of Pivotal Studies to Support Label Claim for PAR and SAR

Per the April 2000 Draft Guidance for Industry “Allergic Rhinitis: Clinical Development Programs for Drug Products” and in accordance with feedback provided by the Division at the pre-IND and End-of-Phase 2 meetings, one SAR and one PAR study can be submitted in support of both the SAR and PAR indications if both trials are adequate and well-controlled Phase 3 clinical trials that demonstrate the safety and effectiveness of the drug for these indications. Nycomed will provide results for 2 pivotal Phase 3 SAR studies (Studies 060-622 and 060-634; 2 weeks in duration) and 1 pivotal Phase 3 PAR study (Study 060-633; 6 weeks in duration) evaluating doses ranging from 80 mcg to 320 mcg in support of the proposed SAR and PAR indications. Key results of these studies are described in Section 3 Clinical Study Background Information above. The 2 pivotal SAR studies include replicated endpoints evaluating improvement in ocular symptoms (rTOSS). The following is the language being proposed for the SAR and PAR indication:

Ciclesonide nasal aerosol is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis (SAR and PAR) in adults and adolescents ≥12 years of age and older.

Does the Division agree that the results of these three Phase 3 studies are adequate to support review of the ciclesonide nasal aerosol NDA for the proposed indication?

Does the Division agree with the proposed labeling text?

FDA Response:

We agree that the clinical development program presented is adequate to support review of a ciclesonide nasal aerosol NDA for the indications of seasonal and perennial allergic rhinitis.

Question 4: ISE Pooling Strategy and Data Presentation

Nycomed proposes to pool efficacy results from the two pivotal SAR studies (Study 060-622 and Study 060-634) as described in the proposed data analysis and reporting plan. Efficacy results from the one pivotal PAR study (060-633) and all efficacy data from supportive studies will be assessed individually. The pooling strategy has been developed in accordance with the August 2008 FDA Guidance entitled “Guidance for Industry - Integrated Summary of Effectiveness.”

The Data Analysis and Reporting Plan for the ISE is provided in Appendix G, and the proposed table of contents for the narrative text of the ISE is provided in Appendix H. In accordance with the April 2009 Guidance for Industry entitled “Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document”, Nycomed anticipates that the narrative text of the ISE will meet the suggested size limitations for Module 2 such that it could also serve as Module 2.7.3, Clinical Summary of Efficacy. The supportive tables, listings, and figures would be provided in item 5.3.5.3, Reports of Analyses of Data from More than One Study. Nycomed understands that a clear explanation of where these items are located is to be provided in both Module 2 and Module 5.

Does the Division agree that only data from the two SAR studies should be pooled for the ISE?

Does the Division agree with the proposed presentation (table of contents) of the ISE narrative and that the ISE narrative, if sufficiently concise, is acceptable as the Module 2.7.3 Clinical Summary of Efficacy?

FDA Response:

Yes, we agree that pooling should be conducted only for the two replicate SAR trials (060-622 and 060-634).

The proposed presentation of the ISE narrative is acceptable.

5.3.2. Safety

Question 5: 6-Month Safety Data

Nycomed proposes to include 8 studies (Studies 060-610, 060-622, 060-633, 060-634, MI-601, MI-602, MI-422, FHP-017) evaluating efficacy and safety, including 2 pivotal SAR studies (Studies 060-622 and 060-634) and 1 pivotal PAR study (Study 060-633) in the initial NDA submission. The duration of exposure in the 8 studies ranges from a single dose to 6 months. The pivotal PAR study (Study 060-633) included a pivotal evaluation of efficacy and safety at 6 weeks. In addition, safety was evaluated at the end of the 6 month double-blind treatment period. An additional 6 month open-label study (Study 060-635) utilizing ciclesonide 160 mcg enrolled only subjects who completed Study 060-633. Taken together, these 2 studies (060-633 and 060-635) will provide 12 months safety data for the ciclesonide 160 mcg dose.

During the End of Phase 2 Meeting held on 15 December 2008, the Division confirmed that long term safety data was needed but advised that the NDA could be submitted with 6 months of safety data (Study 060-633), if the data were acceptable, and that the applicant could provide the remaining 6 months of data (Study 060-635) in the 120-day safety update. Based on Nycomed's and Sepracor's review of the 6-month safety data obtained from Study 060-633, both ciclesonide doses were safe and well tolerated. Further, the safety profile was similar to what has been observed with chronic use of other drugs in the intranasal steroid class.

Based on review of these 6-month data, Nycomed proposes to include results of the 6-month double-blind PAR study (Study 060-633) in the initial NDA filing and to submit the long-term safety study (Study 060-635) and updated ISS in the 120 day safety update. For reference, Appendix J provides a TOC for the ISS that incorporates sections that would be included in the 120 day safety update.

Does the Division agree that the 6 month data are adequate to demonstrate the safety of ciclesonide nasal aerosol, such that Nycomed can submit the NDA with the initial 6 month safety data (Study 060-633) and submit the additional 6 months of safety data (Study 060-635) with the 120 day safety update?

FDA Response:

The submission should include whatever data you consider necessary to support the proposed indication. Based on the summary information provided, the proposed approach is acceptable. However, the overall adequacy of the safety data to support the proposed indication will be a review issue.

Question 6: Scintigraphy Study

At the pre-IND meeting, the CMC Reviewer noted a concern

(b) (4)

(b) (4) On 15 December 2006, in response to this pre-IND issue, Nycomed provided the following background explanation:



Nycomed noted in this response that a PK study would be conducted to examine the systemic exposure of ciclesonide. This pharmacokinetic study (M1-422) that investigated single doses of Alvesco Inhalation Aerosol (320 mcg), Omnaris Nasal Spray (300 mcg) as well as ciclesonide Nasal Aerosol (160 mcg) has been completed. The results demonstrate that, at four times the dose being proposed for commercialization (320 mcg), ciclesonide nasal aerosol exhibits 10 fold less systemic exposure as compared to the Alvesco Inhalation Aerosol (US approved high dose).

Exposure of Ciclesonide Nasal Aerosol (320 mcg) was 3 to 4 fold higher than a 300 mcg dose of Omnaris Nasal Spray (US approved dose is 200 mcg). Nycomed interprets these results as demonstrating that the systemic absorption of the proposed 80 mcg dose of Ciclesonide Nasal Aerosol is likely similar to that of the approved Omnaris Nasal Spray product, supporting the explanation provided above that the product is largely confined to the nasal cavity. If a significant proportion of the product was absorbed through the lungs then the systemic exposure would be expected to be much higher than was observed. To support NDA review and product commercialization, Sepracor is conducting a healthy volunteer scintigraphy study (Study 060-101) in the United Kingdom to characterize the dispersion of single doses of Ciclesonide Nasal Aerosol (160 mcg) and Omnaris Nasal Spray (200 mcg) in the nasal cavity and airways (if any). This study was ongoing as of the proposed clinical cut-off date of 09 July 2010; therefore results are not yet available.

As the study will utilize a single dose of Ciclesonide Nasal Aerosol in 10 healthy volunteers, results are not anticipated to alter the known safety and efficacy profiles of the product. The study will provide information that could be included in Section 12.3,

Pharmacokinetics, of the proposed package insert. Nycomed thus proposes to submit the clinical study report for this scintigraphy study (Study 060-101; see protocol synopsis in Appendix F) and potential revised labeling text in the 120 day safety update. Additionally, results from Study 060-101 would be incorporated into the clinical pharmacology, Module 2.7.2 and the ISS in the 120 day safety update.

Does the Division agree with the proposal to include the scintigraphy study and potential revised labeling text in the 120-day update?

FDA Response:

The proposal to submit the scintigraphy study in the 120-day update appears reasonable. While such a study may be informative from a scientific and regulatory standpoint, it is unlikely that results would be included in the product label.

Discussion:

Sunovion proposed (b) (4). The FDA stated that the Sponsor may provide justification for this proposal in their application; however, it is atypical to include such data. The FDA noted that no other nasal product on the U.S. market has this type of information in the product label. (b) (4)

Therefore, it is highly unlikely that the results (b) (4) would be found acceptable for inclusion in the product label.

Question 7: Growth Velocity Data

The Phase 3 clinical studies included adolescents age 12 to ≤18 years. As such Nycomed proposes to include this patient population in the indication statement of the labeling. In considering the evaluation of ciclesonide on growth velocity in this population we believe existing data are sufficient to fulfill this requirement. In PK Study M1-422, ciclesonide nasal Aerosol at a dose of 320 mcg was shown to have approximately 10-fold less systemic exposure than the Alvesco Inhalation Aerosol. Given the greater systemic exposure seen for the inhalation aerosol, Nycomed proposes that the results of Study 343 regarding effects on growth in children (as summarized in the current Alvesco Inhalation Aerosol and Omnaris Nasal Spray labeling) are applicable to the evaluation of ciclesonide nasal aerosol and are adequate to fulfill the requirement to assess the effects of the drug on growth. Therefore, the currently-approved label language is appropriate for the ciclesonide nasal aerosol product. Study 343 was a multicenter, randomized, double-blind, placebo controlled, non-inferiority study assessing the effects of ciclesonide oral inhalation aerosol (Alvesco) 40 mcg/day and 160 mcg/day administered once daily on growth in children with mild persistent asthma. The report for this study was submitted to the Alvesco NDA 21-658 on 10 July 2007.

Does the Division agree that the available growth study (Study 343), which was accepted by the Division to fulfill the requirement for growth studies for Alvesco Inhalation Aerosol and Omnaris Nasal Spray, provides sufficient data for Ciclesonide Nasal Aerosol such that no further growth studies are required?

FDA Response:

The proposed approach appears reasonable.

Question 8: ISS Pooling Strategy and Data Presentation

Nycomed plans to pool studies according to the strategy described in the proposed ISS data analysis and reporting plan for the NDA and the 120 day safety update (See Appendix I). The proposed pooling approach is designed to provide assessments of safety for short term (ie, 2-6 weeks), chronic (6 months), and long-term (> 6 months) dosing.

Nycomed plans to utilize a clinical cut-off date of 09 July 2010 for availability of clinical data within the original NDA submission. The data analysis and reporting plan (DARP) for the ISS provides analyses for all studies to be included both within the NDA submission and within the 120-day safety update. Nycomed plans to submit the narrative text of the ISS with supportive tables, listings, and figures in Module 5.3.5.3 Reports of Analyses of Data from More than One Study.

Based on the clinical cut-off date, 2 studies will be ongoing at the time of the original NDA submission (Study 060-101 [Scintigraphy study, see Question 6 above] and Study 060-635 [Long-term Safety study; see Question 5 above]; therefore, the Sponsor proposes to include these studies in the 120-day safety update.

A proposed table of contents for the narrative text of the ISS is provided in Appendix J. The table of contents for the narrative text of the ISS includes references to the ongoing studies (060-101 and 060-635) that are proposed to be included in the 120 day update. These references were included in order to provide the FDA with a complete picture of the presentation of the ISS through submission of the 120 day update.

Does the Division agree with the data pooling strategy for the proposed data analysis and reporting plan for the ISS for both the NDA and the 120 day safety update?

Does the Division agree with the proposed presentation of the ISS narrative?

FDA Response:

Yes, we agree with the data pooling strategy to provide assessments of safety for short term (2-6 weeks), chronic (6 months), and long-term (> 6 months) dosing. We agree with the reporting plan for the ISS and proposed presentation of the ISS narrative.

Question 9: Post-Marketing Safety Data

Ciclesonide is currently marketed as an aqueous nasal spray (Omnaris) for the treatment of allergic rhinitis as well as an inhalation aerosol (Alvesco) for the treatment of asthma. For the summary of the post-marketing experience in the ISS, in addition to estimates of patient exposure expressed in person-years, the sponsor plans to provide tabular summaries of postmarketing safety data for both approved products. The summaries will be organized by MedDRA System Organ Class (SOC) and preferred term (PT) and will present the number of the respective event terms reported. In addition, the sponsor plans to provide a listing of serious events. Data elements to be provided in this listing include: date of report, country of origin, reporter category (consumer, HCP, literature), dose, patient age and gender, and event preferred term(s).

Does the Division agree with this approach? In addition, does the Division agree that the data elements to be provided will be sufficient?

FDA Response:

The proposed approach appears to be reasonable. We recommend you also include a data element describing the outcome of events, when available. Depending on the nature of the safety findings reported, additional data may be required.

Discussion:

Sunovion stated that they intend to add a data element providing the outcome of events.

Question 10: Clinical Pharmacology

Studies supporting the human metabolism, intrinsic and extrinsic profile of ciclesonide and special populations have been presented in the Omnaris Nasal Spray NDA (22-004) and Alvesco Inhalation Aerosol NDA (21-658). Nycomed proposes to cross-reference the relevant sections (and reports) in those NDAs in support of this NDA submission. The following three additional clinical studies with PK assessments, one in vitro study, and four analytical method validation studies will be included in the ciclesonide nasal aerosol NDA:

- Study M1-422, a randomized 3-period cross-over PK study comparing systemic exposure to descliclesonide following administration of ciclesonide nasal spray, ciclesonide nasal aerosol and ciclesonide inhalation aerosol,*
- Study M1-601 a randomized double-blind 3 period cross-over study to investigate the PK and PD profile of ciclesonide in 18 healthy and 18 PAR subjects following administration of HFA nasal aerosol, and*
- Study 060-101 (ongoing), an open-label, non-randomized scintigraphy study to assess nasal and pulmonary deposition of a single dose of ciclesonide following administration by nasal aerosol and aqueous nasal spray (proposed to be included in the 120 day safety update; see Question 6 above),*

- **Study 493/2007, an in vitro study to examine the ability of ciclesonide to inhibit human CYP enzymes, and**
- **Study 92/2005, a validation of a LC-MS/MS method for determination of ciclesonide and des-ciclesonide in human serum will be included in the submission [the validation method used in support of Study 178/2005 (CP-036)].**
- **Study 243/2005, a validation of a LC-MS/MS method for determination of ciclesonide and des-ciclesonide in human serum will be included in the submission [the bioanalytical method used in support of Study M1-422 and Study M1-601].**
- **Study VAL-05604, a validation of a LC-MS/MS method to determine ketoconazole in human serum and plasma will be included in the submission [the bioanalytical method used in support of Study 178/2005 (CP-036)].**
- **Study VAL-03402, a validation of a LC-MS/MS method for determination of erythromycin in human plasma will be included in the submission [the bioanalytical method used in support of Study 304/98 (FHP019)].**

Overall, these studies support the previously determined pharmacokinetic profile and exposure for ciclesonide. A summary of these previous findings is presented in Appendix D.

Item 2.7.1 in Module 2 will provide information on the bioanalytical methods used to support the three clinical studies, will reference appropriate sections in the two NDA's cited above, will provide information (Study M1-422) on comparative exposure of ciclesonide nasal aerosol to the aqueous nasal spray (Omnaris) and inhalation aerosol (Alvesco) products and will briefly describe the validated LC-MS/MS method (Study 243/2005).

Item 2.7.2 will provide information on the clinical pharmacology profile of ciclesonide, referencing the NDAs cited above, and will include additional PK assessments from the following studies,

- **Clinical Study M1-601, that provides supplemental data on safety and tolerability,**
- **Clinical Study 060-101 (ongoing) that provides information on target tissue exposure after intranasal administration (proposed for inclusion in the 120 day safety update; see Question 6), and**
- **Study 493/2007, an in vitro assessment of the potential for drug interactions with ciclesonide (study report to be provided in Module 4.2.2.6).**

Nycomed proposes the following approach for the clinical pharmacology sections of the ciclesonide nasal aerosol NDA.

- **Module 2.7.1 and 2.7.2 will be comprised of a summary of the relevant bioanalytical and clinical pharmacology studies conducted with ciclesonide**

- ***A tabular listing of all bioanalytical and clinical pharmacology studies and their submission locations (previous NDA location or current NDA location) will be included in Modules 2.7.1 and 2.7.2, respectively. A comprehensive tabular listing is provided in Appendix E.***
- ***Module 5.3.1.4, Reports of Bioanalytical and Analytical Methods for Human Studies will include only the four new nonclinical studies (92/2005, 243/2005, VAL-03042 and VAL-05604) and that the bioanalytical reports previously submitted in the Alvesco or Omnaris NDAs not be resubmitted.***
- ***Bioanalytical reports for each new clinical study will be included in the corresponding Clinical Study Reports folder.***

Does the Division agree with our proposed approach for submission and cross-reference of bioanalytical and clinical pharmacology studies, and that the studies to be summarized (and cross-referenced) in Module 2.7.1 and 2.7.2 along with the new reports to be included in Module 5.1.3.4 constitute a complete clinical pharmacology package for filing the planned Ciclesonide Nasal Aerosol NDA?

FDA Response:

Your proposed approach appears reasonable. We notice that you do not have PK data for your proposed 80 mcg dose. You may consider characterizing the PK of the 80 mcg dose for labeling purposes.

Discussion:

Sunovion asked the FDA if the PK parameters used at the higher doses can be applicable to the 80 mcg dose. The FDA stated that this appears reasonable and noted that the PK data will be used for labeling purposes. Currently, the FDA is unable to agree on the language to be used in the label at this time.

Question 11: Pediatric Research

The NDA will include studies evaluating the safety and efficacy of ciclesonide for SAR and PAR that enrolled subjects age 12 to ≤18 years in addition to adult subjects. It is proposed that the indication will include this patient population. A proposal for a pediatric waiver for children age 0 to < 2 years and a deferral of studies in children age 2 to 11 years is provided in Appendix K.

Does the Division agree with the proposed pediatric waiver and deferral approach?

FDA Response:

While your proposal appears reasonable, decisions about the waiver and deferral of pediatric study requirements are made during the review of the NDA.

5.3.3. Electronic Submission Questions

Question 12: Location of Datasets and CRFs

Datasets will be provided in the initial ciclesonide nasal aerosol NDA submission for the following Phase 1, 2 and 3 allergic rhinitis studies: Studies FHP-017, M1-422, M1-601, M1-602, 060-610, 060-622, 060-633, and 060-634. Datasets for studies 060-635 and 060-101 are planned to be provided in the 120 day safety update (see above Section 1.8.3.3 Questions 1 and 2). The location of these datasets will be according to the folder structure specified in the FDA's eCTD Study Data Specifications (SDS) document (V. 1.5.1). Subfolders titled "analysis\datasets" and "tabulations\sdm" will contain the analysis and SDTM datasets, respectively, for four studies submitted in CDISC format (060-610, 060-622, 060-633, 060-634).

Subfolders titled "analysis\datasets" and "tabulations\legacy" will contain the analysis datasets and tabulations data for three legacy studies (M1-422, M1-601, M1-602).

Legacy study FHP-017 has one set of datasets, consisting of both analysis and raw data. These datasets will be submitted in a subfolder titled "analysis\datasets". See the screenshot below for the proposed folder structure.

Nycomed proposes to provide the required CRFs for subjects that experienced deaths, serious adverse events, and adverse events leading to subject discontinuation. Other adverse events of interest (i.e., nasal adverse events, etc) will be discussed in narrative form only. Additionally Nycomed proposes to have the study Case Report Forms reside in the respective appendix of the clinical study report in accordance with industry standard. This proposal has been discussed with the e-Sub division at the FDA.

Is the location and directory structure of the datasets acceptable?

FDA Response:

Yes, your proposal is acceptable.

Is the Division in agreement with the proposal for the CRFs to be provided as well as their location?

FDA Response:

Yes, we agree with your proposal.

Question 13: Annotated CRFs

Annotated CRFs for studies 060-610, 060-622, 060-633, 060-634 will be included in the \tabulations\sdm folder. The files will be named blankcrf.pdf, and will contain annotations for the CRF fields to their corresponding locations in the SDTM datasets.

For studies M1-422, M1-601, M1-602, the annotated CRFs will be included in the \tabulations\legacy folder. The files will be named blankcrf.pdf, and will contain

annotations for the CRF fields to their corresponding locations in the legacy tabulations datasets.

For study FHP-017, the annotated CRF will be included in the \analysis\datasets folder. The file will be named blankcrf.pdf, and will contain annotations for the CRF fields to their corresponding locations in the analysis datasets.

Is this proposed format for annotated CRFs acceptable?

FDA Response:

Yes, your proposal is acceptable.

Question 14: Dataset Definitions and Style Sheet

An XML backbone file utilizing the CDISC CRT-DDS version 1.0 schema will be used to organize and describe the datasets. A define.xml file will be utilized in lieu of a define.pdf file for the four studies submitted in SDTM format (060-610, 060-622, 060-633, 060-634). Each define.xml will be located in the same directory as its associated datasets (analysis and SDTM).

For the four legacy studies (FHP-017, M1-422, M1-601, M1-602), a define.pdf file will be supplied to provide the data definitions for both analysis and raw data libraries, as applicable.

For use with the define.xml, the Sponsor plans to include a stylesheet. The stylesheet is based on the define1-0-0.xsl file issued with the Metadata Submission Guidelines Appendix to the SDTM Implementation Guide by CDISC in July, 2007. The Sponsor will also include the define1-0-0.xsd schema file for the define.xml, as well as four supporting files for the stylesheet (file types of .css and .gif). The Sponsor proposes to place the stylesheet and these accessory files in the same folder as the define.xml and the associated datasets.

Does the Agency concur with the Sponsor's plan for the organization of the data definition file and is it acceptable to provide a define.xml in lieu of a define.pdf file for the four studies in CDISC format, and to provide a define.pdf for the four legacy studies?

FDA Response:

Yes, your proposal is acceptable.

Does the Agency agree with the Sponsor's plan to provide a stylesheet and is the proposed location in the eCTD acceptable?

FDA Response:

Yes, your proposal is acceptable.

Question 15: Datasets

Raw clinical data for studies 060-610, 060-622, 060-633, and 060-634 will be provided in SAS version 5 transport format using the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) version 3.1.1. Any instances of nonconformance to the SDTM model will be documented in the supplemental documentation referenced for the define.xml. The file will be named “supplemental.pdf”. SDTM datasets larger than 400 MB will not be divided, as per the FDA’s eCTD SDS V1.5.1 document.

Data from three legacy studies in the clinical program (M1-422, M1-601, M1-602) were acquired from another sponsor who prepared SDTM datasets using an older SDTM format and are not completely compliant to the SDTM model. The Sponsor proposes to submit these as “tabulations\legacy” datasets. Study M1-602 will also have 3 raw datasets submitted with the “SDTM-like” datasets in the “tabulations\legacy” folder. These 3 raw datasets were used to build some analysis datasets (along with the “SDTM-like” datasets), and are being submitted for complete traceability of the source of the analysis datasets. Therefore, for study 602, the “tabulations\legacy” datasets folder will contain a mixture of SDTM-like and raw datasets.

Legacy study FHP-017 has one data library, comprised of both analysis and raw data (non-SDTM, legacy format). This data library will be submitted in the analysis datasets folder.

Analysis datasets for studies 060-610, 060-622, 060-633, and 060-634 will be provided in SAS version 5 transport format and were all created based on using the SDTM data as the source. For analysis datasets that are based from SDTM datasets that are larger than 400 MB (and not divided), we propose to not divide the analysis datasets into subsets of 400 MB or less.

Analysis datasets for legacy studies M1-422, M1-601, and M1-602 will be submitted in SAS version 5 transport files.

Analysis datasets for study FHP-017 will also include all raw data and will be submitted in SAS version 5 transport files in a legacy format.

Is the proposed format regarding the datasets for raw clinical data and analysis acceptable?

FDA Response:

Yes, your proposal is acceptable as long as “SDTM” and “SDTM-like” datasets are correctly reflected in the CRF.

Discussion:

Sunovion asked the FDA if stamps are required, i.e., SDTM or SDTM-like datasets, on the front pages of the annotated CRFs. The FDA asked Sunovion to define “SDTM-like”. The FDA noted that variables have to link to the CRF and there needs to be one to one mapping. Sunovion explained that “SDTM-like” refers to 3 studies that were done in the older version of SDTM which may not have all of the variables as the newer version, but will still connect/link to the CRFs.

Question 16: Statistical Programming Code

The Sponsor intends to provide statistical programming code for the creation of all analysis datasets and all tables, figures and listings for Studies M1-602, 060-610, 060-622, 060-633, 060-634. The Sponsor intends to provide statistical analysis code under the directory “analysis\programs” with subfolders for various types of programs such as “datasets”, “tables”, “figures”, “listings” for each study referenced above. These will be SAS programs (.sas), provided in ASCII format only, as per the FDA’s eCTD SDS V 1.5.1 document.

Is the location and format of the programs identified acceptable?

FDA Response:

Yes, your proposal is acceptable.

Question 17: Patient Profiles

The Sponsor will be providing datasets in CDISC SDTM format for the four Phase 3 studies (Studies 060-610, 060-622, 060-633, and 060-634). It is understood that the Division can generate patient profiles from datasets in this format. Therefore, the Sponsor is requesting a waiver for submission of patient profiles.

Does the Agency agree with this request for a waiver?

FDA Response:

We recommend that you send the patient profiles for serious adverse events along with the datasets in order to expedite the review of your application.

Discussion:

Sunovion stated that they will provide patient profiles.

Question 18: Large Diary Listing

The listing of individual patient data diaries for the full 6 month double-blind treatment period of the long-term safety and efficacy Study 060-633 is extremely large (~ 40,000 pages). It is anticipated that these diaries will also be extremely large in the 6

month safety Study 060-635. As stated above the datasets for these studies will be provided in CDISC SDTM format. The Sponsor proposes to provide the listing of individual patient diary data for the first 6 weeks of the double-blind treatment period (supporting the primary efficacy endpoint) for Study 060-633 in the original NDA and requests a waiver from providing the entire 6 month double-blind period (for Study 060-633 in the NDA and for Study 060-635 in the 120 day update). Individual patient diary data for specified subjects will be made available upon request.

Does the Division agree with the proposal approach for these patient data diaries?

FDA Response:

Yes, your proposal is acceptable.

Additional Comments:

We have the following comments regarding cross referencing information within your electronic submission:

- 1. All tabular listings provided should be linked, preferably.*
- 2. Your option to cross reference information submitted to another application should include a cross reference document under module 1.4.4 (cross reference to other applications) in the eCTD section, and should also include cross application links in addition to the cross reference document.*
- 3. Prior to using cross application links in an application, you should submit a sample to ensure they are able to successfully use cross application links. In order to use cross application links, both applications would need to be in eCTD format and reside on the same server. To submit an eCTD sample to test cross application linking, you would need to request two eCTD sample application numbers for the cross application linking. Please refer to the Sample Process page <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. For information and instructions, send an email to esub@fda.hhs.gov.*

Discussion:

Sunovion stated that they submitted the eCTD sample to test cross application linking on November 2, 2010, and have had no reply to date. Sunovion asked the FDA if they will be able to manually cross reference if the test sample does not work. The FDA stated that this is acceptable.

Sunovion stated that the Alvesco NDA 21-658 was submitted in eNDA format and asked the FDA if it is acceptable if they are unable to provide electronic links to the Alvesco NDA in the Ciclesonide HFA Aerosol NDA application. The FDA stated that this is acceptable as long as a cross reference document is provided under module 1.4.4.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

Clarifying document sent via e-mail on November 1, 2010, and officially submitted on November 5, 2010.

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INTRODUCTION

We would like to thank the Division for providing comments to our clinical pre-NDA meeting questions in such a timely manner. As our targeted NDA filing date of late Q1 2011 nears, we appreciate the opportunity to discuss the Ciclesonide Nasal Aerosol program with the Division at our clinical pre-NDA meeting on November 3, 2010. We have prepared this document to facilitate the discussion at the meeting. We have requested follow up discussion regarding the Division's comments to Questions 2, 10, 15, and the "Additional FDA Comments" regarding cross referencing information. Additionally, we have provided clarification comments to Questions 1, 6, 9, and 17.

QUESTION 1: ADEQUACY OF NONCLINICAL PROGRAM AND PLANS TO CROSS-REFERENCE

Does the Division agree with our proposed approach for submission and cross-reference of nonclinical studies, and that the studies to be summarized (and cross-referenced) in Module 2 along with the new reports to be included in Module 4 constitute a complete nonclinical package for filing the planned Ciclesonide Nasal Aerosol NDA?

FDA Response:

Your proposed approach for submission and cross reference of nonclinical studies seems reasonable and constitutes a complete nonclinical package for filing the Ciclesonide Nasal Aerosol NDA.

Additional Non-Clinical Comment:

For your NDA submission, provide structures of impurities and intermediates of the drug substance and drug product. Monitor impurities and degradation products of all active ingredients. Refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R)] and degradants in drug products [ICH Q3B(R)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants. Impurities or intermediates that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" (December 2008) for assessments of impurities to support clinical studies for an IND and NDA.

Sunovion Comment:

The drug product for the ciclesonide nasal aerosol is identical (i.e. same canister) to that used in NDA 21-658 (ALVESCO); impurities and degradants in the drug product have been identified and characterized appropriately. For details of the characterization of impurities in drug substance and drug product, please reference NDA 21-658 ALVESCO Original Submission (December 22, 2003) Section 2.6.7 Toxicology Tabulated Summary, Table 4 Drug Substance and NDA 22-004 OMNARIS Serial 0000, Section 2.6.7 Toxicology Tabulated Summary, Table 4 Drug Substance. These tables list the drug substance impurities assessed in nonclinical studies to support the ciclesonide submissions.

The quality of ciclesonide drug substance has been assessed according to ICH guideline Q3A. Batches of ciclesonide drug substance used in nonclinical safety studies were typical of the material proposed for commercial use of the nasal aerosol formulation, and also that used in clinical trials, in terms of impurity profile. All impurities were present in nonclinical drug substance batches at comparable or greater concentration than those proposed in the specification for release of commercial drug substance.

The toxicity of extractables/leachables for the ciclesonide MDI is mentioned in 3.2.P.2 Pharmaceutical Development and is evaluated in DMF (b) (4). (b) (4) has conducted a toxicological evaluation of the leachables present in HFA-134a ciclesonide MDI placebo formulations following the approaches described in applicable FDA Guidance. There are no toxicological safety concerns for the product and the control limits stipulated in the specifications also pose no safety issues.

Overall, the impurities of ciclesonide and ciclesonide nasal aerosol have been identified and qualified where appropriate. The specification limits for impurities, degradation products, and leachables are supported by toxicological data and risk assessment.

QUESTION 2: DOSE FOR COMMERCIALIZATION

Does the Division agree that the 80 mcg dose is the appropriate recommended dose on which the proposed label should be based?

FDA Response:

Yes, we agree, pending review of the data. We note that the summary information provided indicates that no clear dose response was observed, which will be a review issue.

Sunovion Comment:

Nycomed is developing the Dose Justification section of the ISE and is planning to provide summary information on the following to support this justification:

- Dose ranging study efficacy data (Study M1-602; 80, 160, 320 mcg)
- Pivotal efficacy data (Studies 060-622, 060-634, and 060-633; 80 and 160 mcg)
- Known data with regard to dose response for approved intranasal corticosteroids including Omnaris Nasal Spray

Does the Division agree that this approach is adequate to address their comment regarding dose response?

QUESTION 3: SCOPE OF PIVOTAL STUDIES TO SUPPORT LABEL CLAIM FOR PAR AND SAR

Does the Division agree that the results of these three Phase 3 studies are adequate to support review of the ciclesonide nasal aerosol NDA for the proposed indication?

Does the Division agree with the proposed labeling text?

FDA Response:

We agree that the clinical development program presented is adequate to support review of a ciclesonide nasal aerosol NDA for the indication of seasonal and perennial allergic rhinitis.

Sunovion Comment:

No further questions.

QUESTION 4: ISE POOLING STRATEGY AND DATA PRESENTATION

Does the Division agree that only data from the two SAR studies should be pooled for the ISE?

Does the Division agree with the proposed presentation (table of contents) of the ISE narrative and that ISE narrative, if sufficiently concise, is acceptable as the Module 2.7.3 Clinical Summary of Efficacy?

FDA Response:

Yes, we agree that pooling should be conducted only for the two replicate SAR trials (060-622 and 060-634). The proposed presentation of the ISE narrative is acceptable.

Sunovion Comment:

No further questions.

QUESTION 5: 6-MONTH SAFETY DATA

Does the Division agree that the 6 month data are adequate to demonstrate the safety of ciclesonide nasal aerosol, such that Nycomed can submit the NDA with the initial 6 month safety data (Study 060-633) and submit the additional 6 months of safety data (Study 060-635) with the 120 day safety update?

FDA Response:

The submission should include whatever data you consider necessary to support the proposed indication. Based on the summary information provided, the proposed approach is acceptable. However, the overall adequacy of the safety data to support the proposed indication will be a review issue.

Sunovion Comment:

No further questions.

QUESTION 6: SCINTIGRAPHY STUDY

Does the Division agree with the proposal to include the scintigraphy study and potential revised labeling text in the 120-day update?

FDA Response:

The proposal to submit the scintigraphy study in the 120-day update appears reasonable. While such a study may be informative from a scientific and regulatory standpoint, it is unlikely that results would be included in the product label.

Sunovion Comment:

We understand that the scintigraphy study can be submitted in the 120 day update. Preliminary results have been obtained on this study since submission of the briefing document. The data show that more than 97% of administered ciclesonide was detected in the nasal cavity and less than 3% in the lung. No ciclesonide was detected in the esophagus or stomach. Statements such as the prior two sentences characterizing the overall distribution of the drug may be informative for the prescriber. Nycomed plans to propose a statement in the product label for the Division's consideration during the NDA review.

QUESTION 7: GROWTH VELOCITY DATA

Does the Division agree that the available growth study (Study 343), which was accepted by the Division to fulfill the requirement for growth studies for Alvesco Inhalation Aerosol and Omnaris Nasal Spray, provides sufficient data for Ciclesonide Nasal Aerosol such that no further growth studies are required?

FDA Response:

The proposed approach appears reasonable.

Sunovion Comment:

No further questions.

QUESTION 8: ISS POOLING STRATEGY AND DATA PRESENTATION

Does the Division agree with the data pooling strategy for the proposed data analysis and reporting plan for the ISS for both the NDA and the 120 day safety update? Does the Division agree with the proposed presentation of the ISS narrative?

FDA Response:

Yes, we agree with the data pooling strategy to provide assessments of safety for short term (2-6 weeks), chronic (6 months), and long-term (>6 months) dosing. We agree with the reporting plan for the ISS and proposed presentation of the ISS narrative.

Sunovion Comment:

No further questions.

QUESTION 9: POST MARKETING SAFETY DATA

Does the Division agree with this approach? In addition, does the Division agree that the data elements to be provided will be sufficient?

FDA Response:

The proposed approach appears to be reasonable. We recommend that you also include a data element describing the outcome of events, when available. Depending on the nature of the safety findings reported, additional data may be required.

Sunovion Comment:

We agree to add a data element providing the outcome (when available) of events to the listing of serious adverse events. We have no further questions.

QUESTION 10: CLINICAL PHARMACOLOGY

Does the Division agree with our proposed approach for submission and cross-reference of bioanalytical and clinical pharmacology studies, and that the studies to be summarized (and cross-referenced) in Module 2.7.1 and 2.7.2 along with the new reports to be included in Module 5.1.3.4 constitute a complete clinical pharmacology package for filing the planned Ciclesonide Nasal Aerosol NDA?

FDA Response:

Your proposed approach appears reasonable. We notice that you do not have PK data for your proposed 80 mcg dose. You may consider characterizing the PK of the 80 mcg dose for labeling purposes.

Sunovion Comment:

The population PK analysis, detailed in the Omnaris Nasal Spray NDA 22-004, utilized a linear PK model with first order absorption, thus suggesting dose proportional changes in exposure. We believe that relevant pharmacokinetic parameters such as half-life, are likely to be dose-independent. Consequently we propose to utilize PK parameters obtained from higher dose levels of ciclesonide nasal aerosol as representative of an 80 mcg dose and would suffice for labeling purposes. We also present proposed label text for your consideration:

(b) (4)

Does the Division agree with this approach to characterize the PK of ciclesonide nasal aerosol in the product labeling?

QUESTION 11: PEDIATRIC RESEARCH

Does the Division agree with the proposed pediatric waiver and deferral approach?

FDA Response:

While your proposal appears reasonable, decisions about the waiver and deferral of pediatric study requirements are made during the review of the NDA.

Sunovion Comment:

No further questions.

QUESTION 12: LOCATION OF DATASETS AND CRFS

Is the location and directory structure of the datasets acceptable?

FDA Response:

Yes, your proposal is acceptable.

Sunovion Comment:

No further questions.

QUESTION 13: ANNOTATED CRFS

Is this proposed format for annotated CRFs acceptable?

FDA Response:

Yes, your proposal is acceptable.

Sunovion Comment:

No further questions.

QUESTION 14: DATASET DEFINITION AND STYLE SHEET

Does the Agency concur with the Sponsor's plan for the organization of the data definition file and is it acceptable to provide a define.xml in lieu of a define.pdf file for the four studies in CDISC format, and to provide a define.pdf for the four legacy studies?

FDA Response:

Yes, your proposal is acceptable.

Sunovion Comment:

No further questions.

QUESTION 15: DATASETS

Is the proposed format regarding the datasets for raw clinical data and analysis acceptable?

FDA Response:

Yes, your proposal is acceptable as long as “SDTM” and “SDTM-like” datasets are correctly reflected in the CRF.

Sunovion Comment:

We interpret the above response such that on the Annotated CRF (blankcrf.pdf) for each study, you would like to see a stamp, such as "SDTM datasets", on the front page of the Annotated CRFs and define.xml files for the 4 SDTM studies (610, 622, 633, 634), and "SDTM-like datasets" on the front page of the Annotated CRFs and define.pdf files for the 4 legacy studies (FHP017, M1-422, M1-601, M1-602).

Please confirm if our interpretation is correct.

QUESTION 16: STATISTICAL PROGRAMMING CODE

Is the location and format of the programs identified acceptable?

FDA Response:

Yes, your proposal is acceptable.

Sunovion Comment:

No further questions.

QUESTION 17: PATIENT PROFILES

Does the Agency agree with this request for a waiver?

FDA Response:

We recommend that you send the patient profiles for cases of death, serious adverse events, and events of nasal septal perforation and nasal ulceration, along with the datasets in order to expedite the review of your application.

Sunovion Comment:

We agree to send the patient profiles for cases of death, serious adverse events, and events of nasal septal perforation and nasal ulceration, for all applicable studies along with the datasets. No further questions.

QUESTION 18: LARGE DIARY LISTING

Does the Division agree with the proposed approach for these patient data diaries?

FDA Response:

Yes, your proposal is acceptable.

Sunovion Comment:

No further questions.

ADDITIONAL FDA COMMENTS:

We have the following comments regarding cross referencing information within your electronic submission:

1. All tabular listings provided should be linked, preferably.
2. Your option to cross reference information submitted to another application should include a cross reference document under Module 1.4.4 (Cross reference to other applications) in the eCTD section, and should also include cross application links in addition to the cross reference document.
3. Prior to using cross application links in an application, you should submit a sample to ensure they are able to successfully use cross application links. In order to use cross application links, both applications would need to be in eCTD format and reside on the same server. To submit an eCTD sample to test cross application linking, you would need to request two eCTD sample application numbers for the cross application linking. Please refer to the Sample Process page <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. For information and instructions, send an email to esub@fda.hhs.gov.

Sunovion Comment:

1. Links are planned for all tabular listings where feasible (see #3 Sunovion Comment below).
2. A cross reference document under Module 1.4.4 is planned and will include links where feasible (see #3 Sunovion Comment below).
3. The vast majority of the cross application references will be to the Omnaris Nasal Spray NDA (i.e., 198 nonclinical study reports) with a few studies cross referenced from the Alvesco Inhalation Aerosol NDA (i.e., 8 nonclinical study reports). Regarding using cross application links, the initial Alvesco Inhalation Aerosol NDA was originally submitted by Aventis Pharmaceuticals (Dec 2003), in eNDA format, NOT in eCTD format. As such cross application links are not considered feasible. In this NDA, Nycomed plans to provide manual cross reference information for Alvesco studies by including the NDA number, original submission, and section number or study number.

Does the Division consider the proposed manual cross reference strategy for the Alvesco studies referenced in the Ciclesonide Nasal Aerosol NDA acceptable?

Regarding using cross application links, the Omnaris Nasal Spray NDA was originally submitted by Altana Pharma (Dec 2005), in eCTD format. The feasibility of using cross application links to this NDA is being tested. If cross application links to the Omnaris Nasal Spray application are determined to be feasible, they will be utilized in the Ciclesonide Nasal Aerosol NDA. If it is not found to be feasible, it is proposed to provide manual cross reference information as is proposed for the Alvesco cross referenced study reports. Nycomed plans to provide manual cross reference information for Omnaris studies by including the NDA number, sequence number, and section number or study number.

If the cross application linking is NOT found to be feasible, does the Division consider the proposed manual cross reference strategy for the Omnaris Nasal Spray studies referenced in the Ciclesonide Nasal Aerosol NDA acceptable?

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Initialed: Pippins/ November 17, 2010
Limb/ November 18, 2010
Whitehurst/ November 16, 2010
Topper/ November 16, 2010
Zhou/ November 19, 2010
Buenconsejo/ November 19, 2010
Fan/ November 17, 2010
Xu/ November 17, 2010
Gooding/ November 16, 2010
Chowdhury/ December 2, 2010

Finalized: CCJ/ December 2, 2010

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/s/

COLETTE C JACKSON
12/02/2010

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: End-of-Phase 2
Meeting Date and Time: December 15, 2008, 1:00-2:00 PM
Meeting Location: via teleconference
Application Number: IND 74,674
Product Name: Ciclesonide HFA Aerosol
Received Briefing Package November 12, 2008
Sponsor Name: Sepracor, Inc.
Meeting Requestor: Renee Carroll
Director, Regulatory Affairs
Meeting Chair: Badrul A. Chowdhury, MD, PhD
Division Director
Meeting Recorder: Colette Jackson
Regulatory Health Project Manager
Meeting Attendees:

FDA Attendees

Office of Drug Evaluation II

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary and Allergy Products

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Wei Qui, PhD, Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

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Sponsor Attendees

Sepracor, Inc.

Joseph Smith MD, Senior Director, Clinical Research, Sepracor

Paul McGlynn PhD, Senior Director, Program Management, Sepracor

Fred Bode MD, Senior Director Clinical Research, Sepracor

Renee Carroll, Director, Regulatory Affairs, Sepracor

Raymond Claus, Director, Biostatistics, Sepracor

Stewart Mueller, Senior Vice President, Regulatory Affairs and Quality Assurance, Sepracor

David Reasner PhD, Senior VP, Biostatistics, Data Management, and Health Outcomes, Sepracor

Mark A. Wingertzahn PhD, Head of US Development, Nycomed

1.0 BACKGROUND

Sepracor, Inc. submitted a Type B meeting request dated October 3, 2008, to discuss the proposed Phase III clinical development plans for adolescents and adults 12 years of age and older for the indications of seasonal and perennial allergic rhinitis. Sepracor's briefing package was submitted on November 12, 2008. Upon review of the briefing package, the Division responded to Sepracor's questions via fax dated December 7, 2008. The content of the fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response under Section 2.0, including any changes in our original position. Sepracor's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2.0 DISCUSSION

Question 1: *Based on the results of Study M1-602 does the Division agree that the 160 mcg and 80 mcg doses of ciclesonide HFA nasal aerosol are the appropriate doses for further testing in the Phase III clinical development program?*

FDA Response:

Yes, your approach is reasonable. However, depending on the results of the phase 3 trials you may need to test lower doses in the pediatric population.

Question 2: *Will the criteria in the PAR (060-632) protocol sufficiently ensure that the primary target population of PAR will be enrolled, and if so, does the Division agree that this trial could be controlled throughout the year?*

FDA Response:

You can enroll patients any time that you think is appropriate. However, the subjects must have documentation of their allergic status to assure that testing the efficacy of a treatment for PAR is not conducted during a season in which allergens to which they are allergic are prevalent.

Question 3: *Based on the above findings, is the division in agreement that a long-term safety trial in PAR patients 12 years of age and older will adequately fulfill the long-term safety requirement for this clinical program?* (b) (4)

FDA Response:

No we do not agree. The preliminary data submitted suggest that ciclesonide HFA nasal spray has a better efficacy profile compared to ciclesonide aqueous suspension and it is possible that the local safety profile may be different. A study duration of up to 52 weeks may be necessary to assess the local safety of your product. Include a placebo arm in your safety study in order to evaluate the long term safety of your product. Without a placebo, all adverse events will be attributable to ciclesonide and included as such in the product label.

Discussion:

Sepracor asked the Division to outline their concerns for the long term safety trial. Sepracor referred to the approval of the Omnaris and Alvesco products and noted that both products had comprehensive long term safety trials provided in their submissions. Sepracor also noted that they have provided dose ranging and PK information to the Division for the ciclesonide HFA aerosol product. The Division stated that the data submitted in the briefing package shows increased absorption in the nasal passages in the PK studies and the Division is concerned with local effects. The formulation is different than that for Omnaris and Alvesco, and Sepracor needs to evaluate local safety such as the presence of erosions, bleeding, epistaxis, perforations, etc. Sepracor stated that the erosion AE shown with the data can easily present within 12 weeks and questioned why the need for a 12 month study. The Division stated that a long term controlled safety study is needed and suggested that Sepracor could plan for a one year study, but look at

the 6 month data and, if it the data are acceptable, they could submit the NDA with plans to submit the one year data with the 4-month safety update.

Sepracor asked if they conduct a one year study if it would be acceptable to do an open label study on the last 6 months of the study with 100 patients. The Division stated that it is up to Sepracor, but that a controlled study is preferred since for an uncontrolled study, all adverse events would be attributable to the ciclesonide.

Question 4: *Does the Division agree that administration of e-diaries, which includes follow-up compliance calls by the site, daily if necessary, along with clinic visit every month will sufficiently ensure documentation of compliance?*

FDA Response:

The e-diaries appear to be a helpful tool in the assessment of compliance and can be one of the methods used to assess compliance. You will need to describe the e-diary and the methods used to validate its accuracy in the NDA submission. You should still evaluate efficacy to assure compliance. As stated in the response to question 3, a placebo-controlled study safety study should be conducted so that an adequate assessment of safety can be made. With a placebo control it would be feasible to assess efficacy to support compliance. You may consider conducting your long term safety study as an extension of the 6-week PAR study (study 632) and continue treatment and follow up of these subjects for up to a year.

Question 5: *Does the Division agree with this approach to validating the dose actuation indicator?*

FDA Response:

Your proposal is reasonable. However, for the NDA submission, we would also like you to validate the dose counter/indicator mechanism by measuring the physical weights of the nasal canister and match that with the dose counter in a separate in vitro study. This should be done like the study conducted for the Alvesco drug product.

Question 6: *Does the Division agree that the study outlined here will be sufficient to meet both the ciclesonide HFA nasal aerosol HPA axis study requirement as well as Phase IV commitment for the ciclesonide aqueous nasal spray program?*

FDA Response:

We concur with the doses chosen, and the overall design appears to be adequate. However, in order to satisfy the phase 4 commitment for ciclesonide nasal spray program you need to include patients 12 years and older in the HPA axis study.

Question 7: *Does the Division agree that the measures outlined in study 060-610 are adequate for monitoring and assuring compliance?*

FDA Response:

No, we do not agree. You should include assessment of efficacy and, if feasible, PK measurements in the study to assure compliance.

Question 8: *Dose the Division concur with the above statistical methodology to be employed in the 060-610 trial?*

FDA Response:

The purpose of the HPA-axis study is to estimate, quantitatively, the effects of ciclesonide on adrenal function. The results will be described (compared to placebo) in the clinical pharmacology section of the label without statements on non-inferiority.

Question 9: *Does the Division agree that the proposed Phase III clinical program presented here will adequately support an NDA in adolescents and adults 12 years of age and older with support from the Phase I and II completed clinical studies and previous data obtained from ciclesonide inhalation aerosol (Alvesco) and ciclesonide aqueous nasal spray (Omnaris) program?*

FDA Response:

In general two SAR studies and one PAR study are sufficient to support efficacy for an SAR and PAR indication. Therefore, you have sufficient studies to support efficacy provided that they all show the desired result. Refer to the responses to questions 3 and 4 above regarding the long-term safety and to the responses to questions 6 and 7 regarding the HPA axis study for additional comments.

Additional Clinical Pharmacology Comment:

In study 060-610, consider PK determination of the active moieties at the end of the study to further explore the PK/PD (PK/cortisol levels, side effects) relationship.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Drafted by: CCJ/ January 9, 2009
Initialed: Gilbert-McClain/ January 11, 2009
Peri/ January 12, 2009
Zhou/ January 13, 2009
Li/ January 13, 2009
Qiu/ January 13, 2009
Chowdhury/ January 14, 2009

Finalized: CCJ/ January 14, 2009

Linked Applications

Sponsor Name

Drug Name / Subject

IND 74674

SEPRACOR INC

CICLESONIDE HFA NASAL SPRAY

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

01/14/2009



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 9, 2008

To: Cheryl Czachorowski for George Chen	From: Colette Jackson
Company: Nycomed	Division of Pulmonary and Allergy Products
Fax number: 973-236-1695	Fax number: 301-796-9718
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Subject: IND 74,674 Responses to Meeting Questions

Total no. of pages including cover: 14

Comments:

Document to be mailed: YES ☒ NO

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IND 74,674
Ciclesonide HFA Nasal Spray
Nycomed

Attached are the FDA responses to your questions (in bold italics) regarding Ciclesonide HFA Nasal Spray. You have the option of canceling our meeting of January 15, 2008 (or change it to a teleconference), if our answer is clear to you. If you choose to have the meeting (or change it to a teleconference), we will be prepared to clarify any questions you have regarding our response. However, please note that if there are any major changes to your development plan (based upon our response herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please notify the Division as soon as possible if you would like to cancel the meeting.

2.1 Pharmaceutical Development (3.2.P.2)

Question 1: Does the Division concur that the proposed list of characterization studies for this nasal MDI product is complete or are there additional studies to be considered?

FDA Response:

Your proposal is reasonable.

Question 2: Does the Division concur with the sponsor's proposal not to repeat these four studies for the ciclesonide HFA Nasal Aerosol product?

FDA Response:

Your proposal is reasonable.

2.2 Drug Product Specifications (3.2.P.5)

Question 3: Does the Division agree with the justification that (b) (4) may be omitted as regulatory release and stability tests for this Ciclesonide HFA Nasal Aerosol product?

FDA Response:

Yes, we agree.

Question 4: Does the FDA concur with maintaining run and record for the DSD and PSD tests for Ciclesonide HFA Nasal Aerosol during Phase III as part of the primary stability studies? Further, does the FDA concur with the

strategy for proposing DSD alone as the regulatory test for monitoring the quality of the solution drug product?

FDA Response:

Your proposal to run and record the DSD and PSD tests for the drug products is acceptable. However update the IND with the results as they become available with the phase 2 batch results. The regulatory specifications will be agreed upon during the review of the NDA.

Question 5: Does the FDA concur with the Sponsor's approach to assigning acceptance criteria for the Spray Content Uniformity test during Phase III?

FDA Response:

Your proposal to defer assigning the label claim for the drug products is acceptable. However update the IND with the phase 2 batch results. The regulatory specifications will be agreed upon during the review of the NDA.

Question 6: Based upon the successful execution of the spray pattern protocol provided, does the FDA concur that this method can be used:

- *by the supplier to release the nasal actuator in place of the drug product release test?*
- *to test actuators using placebo only?*
- *to test at one spray distance?*

FDA Response:

Your proposal is reasonable as long as there is adequate change control protocol between the supplier, fabricator, and you. However provide a justification for this approach during the review of the NDA. Spray Pattern results (b) (4) should be submitted to the NDA.

Question 7: Does the FDA have additional comments concerning the proposed drug product specifications?

FDA Response:

Your proposed specifications seem reasonable however they will be evaluated at the NDA stage. The proposed acceptance criteria for spray content uniformity should be consistent with the recommendations of the draft MDI/DPI guidance. Note that an extractables-leachables correlation from the Nasal Actuator should be demonstrated. We note that the actuators used for the Oral and Nasal products are different.

2.3 Container Closure System (3.2.P.7)

Question 8: *Does the FDA agree that a dose actuation indicator is not required for this product?*

FDA Response:

The Agency typically recommends that MDIs for oral inhalation incorporate a dose actuation indicator early in the development program. You may also choose to develop them for your nasal products. Since your device incorporates the dose indicator already, we recommend that this be carried forward during the phase 3 program. The indicator should be held to the same standards as the orally inhaled MDIs. You will need to do a clinical in-use study to develop the product with a dose counter/indicator.

Question 9: *Does the FDA concur with using this actuator stability program?*

FDA Response:

Your proposal for the actuator stability program is reasonable. Note that the whole drug product should be used for the primary stability batches.

2.4 Drug Product Stability Protocol (Section 3.2.P.8)

Question 10: *Is the primary stability protocol with full ex-nasal actuator testing along with supporting Ciclesonide HFA MDI chemical data adequate to support approval of the expiration dating period for Ciclesonide HFA Nasal Aerosol Spray?*

FDA Response:

Your proposed testing approach is reasonable however the adequacy of the shelf life will be a review issue.

Question 11: *Does the proposal to submit (b) (4) ex-nasal actuator real-time data according to the primary stability protocol along with the 24 months of chemical stability data for the inhaled Ciclesonide MDI drug product, which shows this to be chemically very stable drug product, adequate to support a 24-month expiry period for this product?*

FDA Response:

Your proposed submission approach is reasonable however the adequacy of the shelf life will be a review issue. Note that extrapolation of non-numeric data (such as DSD, PSD, etc.) is not possible using linear regression. Therefore extrapolating (b) (4) data for PSD, DSD, etc. to 24 months may not be possible.

If you have any questions, contact Colette Jackson, Regulatory Health Project Manager,
at 301-796-1230.

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Filename: 74674 January 15 2008 CMC EOP2 Q and A

Linked Applications

Sponsor Name

Drug Name

IND 74674

ALTANA

CICLESONIDE HFA NASAL SPRAY

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

01/09/2008