CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202129Orig1s000

CHEMISTRY REVIEW(S)

Chemistry Review Cover Sheet

NDA 202129
Tradename (ciclesonide) nasal Aerosol
Arthur B. Shaw, Ph.D.
DNDQA III/Branch VIII/DPARP

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Reference ID: 3069839

Chemistry Review Data Sheet

1. NDA 202129

2. REVIEW #: 3

3. REVIEW DATE: January 10, 2012

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Date	Comment
Original	03/19/2011	None
IR via e-mail	07/11/2011	Request SAS data set supporting comparison between V1 and V2 actuators.
Amendment	07/22/2011	Response to 7/11/2011 IR Letter
IR via e-mail	10/04/2011	Request BE profile comparison and SAS datasets supporting comparison between V1 and V2 actuators.
Amendment BC	10/21/2011	Response to 10/21/2011 IR Letter
Chem review #1	12/23/2011	Approvable pending submission of post-approval commitment to re-design a more rugged actuator
IR Letter	12/23/2011	Request for post-approval commitment to re-design a more rugged actuator
Secondary Chem review	12/28/2011	Approvable pending submission of a revision to the APSD acceptance criteria
IR Letter	01/01/2012	Request to revise APSD acceptance criteria
Amendment	1/2/2012	Commitment to explore alternative actuator designs to improve robustness
Amendment	1/6/2012	Revision of acceptance criteria for APSD
Review #2	1/9/2012	Recommend approval

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Amendment	1/9/2012	Revised commitment to explore alternative actuator designs to improve robustness

Reference ID: 3069839

7. NAME & ADDRESS OF APPLICANT:

Name:	Nycomed GmbH
Address:	Byk-Gulden-Strasse 2 78467 Konstanz Germany

NAME & ADDRESS OF AGENT:

Name:	Sunovion Pharmaceuticals Inc
Address:	84 Waterford Dr. Marlborough MA 01752
Representative:	Reneé M Carroll, MS, RAC, Senior Director, Regulatory Affairs
Telephone:	Telephone: (508) 357-7598 Fax: (508) 357-7491
E-mail	renee.carroll@sunovion.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Under review
b) Non-Proprietary Name (USAN): ciclesonide
c) Code Name/# BYK20426, B9207-015
d) Chem. Type/Submission Priority
- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Aerosol

12. STRENGTH/POTENCY: 37 µg/actuation (ex-actuator)

(b) (4)

13. ROUTE OF ADMINISTRATION: Nasal Inhalation

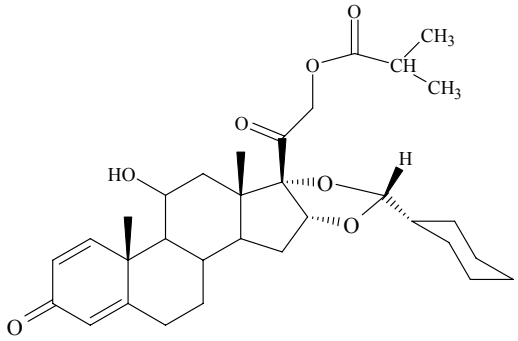
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(2'R)-2'Cyclohexyl-11b-hydroxy-21-isobutyryloxy-16b*H*-dioxolo[5',4':16,17]

Reference ID: 3069839

pregna-1,4-diene-3,20-dione



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Chem Review #1

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,391	Ciclesonide MDI
NDA	19658	Alvesco (ciclesonide) Inhalation Aerosol

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	**ACCEPTABLE**	12/06/2011	Meiyu Shen
EES	Acceptable	22-Apr-2011	N/A
Methods Validation	Not submitted		
DMETS	Proprietary name	Under review	
EA	N/A		
Microbiology	**ACCEPTABLE** for NDA 21658	04-Apr-2004	Bryan Riley

Reference ID: 3069839

The Chemistry Review for NDA 202129

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The application may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.
The applicant committed to developing a more rugged actuator/dose counter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance
The drug substance is a corticosteroid and is a white to yellowish powder. It is freely soluble in ethanol, insoluble in water, and soluble in ethanol. It is synthesized [redacted] (b) (4) yielding the R-epimer. The complete CMC information is contained in DMF [redacted] (b) (4), which has been recently updated, reviewed and found acceptable. It is manufactured by [redacted] (b) (4). This site was found **ACCEPTABLE** in the EER.

2. Drug Product
The drug product is a solution of ciclesonide in [redacted] (b) (4) dehydrated ethanol with HFA-134a (a non-CFC propellant) as the propellant. The solution is filled into an [redacted] (b) (4) canister to provide 30 or 60 actuations and sealed with a metering valve. A plastic actuator, which includes a dose counter, is included as part of the finished drug product. The valve is designed to deliver the drug accurately at 37 µg/actuation. (ex-actuator). The [redacted] (b) (4) canister and valve combination are exactly the same as those used in the approved drug product, Alvesco (ciclesonide) Inhalation Aerosol. The only difference is in the actuator, which is designed to deliver the drug to the nose.

The Pharmaceutical Development Report (PDR) supports the choice of ethanol content, the number of priming shots required (in the label), and the lack of a need for shaking prior to use [redacted] (b) (4)
The specifications include tests and acceptance criteria for ciclesonide content, alcohol content leak rate, valve delivery, impurities, Aerodynamic Particle Size Distribution (APSD) and delivered dose ex-actuator (Spray

Reference ID: 3069839

Content Uniformity =SCU).

The levels of most impurities are below (b) (4) and do not change on storage. The only impurity present on significant amounts (b) (4) has been qualified (b) (4)
The drug is stable, showing no trends over time for ciclesonide content, impurities, APDS or SCU.

The assembled inhaler includes the canister containing the drug product and the actuator, which has a dose counter built in. Drop tests show that a) the canister can be separated from the actuator and b) the does counter can give incorrect counts after dropping. Therefore the applicant was asked to commit to develop a new actuator which is more rugged.

The applicant has provided a Comparability Protocol to qualify future redesigns of the actuator. Changes that may impact actuator performance in terms of delivery of the drug will be filed as CBE30 and will include testing for APSD, SCU and other important parameters. Changes that may affect the dose indicator function will be submitted as CBE0 supplements and will include testing of count accuracy, drop testing and other parameters. Other changes that do not have the potential to affect either the actuator performance or the dose counter will be filed as Annual Reports. The Comparability protocol is acceptable.

The drug product is manufactured by (b) (4) . This site is **ACCEPTABLE** in EES. The valve is manufactured by (b) (4) . The actuator is manufactured by Aptar (b) (4)

B. Description of How the Drug Product is Intended to be Used
The proposed drug product label is for "treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older."

C. Basis for Approvability or Not-Approval Recommendation
The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach its target site in the nose consistently up to the labeled number of actuations on the label.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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

Reference ID: 3069839

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/s/

ARTHUR B SHAW
01/10/2012

PRASAD PERI
01/10/2012
I concur

Chemistry Review Cover Sheet

NDA 202129
Tradename (ciclesonide) nasal Aerosol
Arthur B. Shaw, Ph.D.
DNDQA III/Branch VIII/DPARP

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Reference ID: 3069082

Chemistry Review Data Sheet

1. NDA 202129

2. REVIEW #: 2

3. REVIEW DATE: January 9, 2012

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Date	Comment
Original	03/19/2011	None
IR via e-mail	07/11/2011	Request SAS data set supporting comparison between V1 and V2 actuators.
Amendment	07/22/2011	Response to 7/11/2011 IR Letter
IR via e-mail	10/04/2011	Request BE profile comparison and SAS datasets supporting comparison between V1 and V2 actuators.
Amendment BC	10/21/2011	Response to 10/21/2011 IR Letter
Chem review #1	12/23/2011	Approvable pending submission of post-approval commitment to re-design a more rugged actuator
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IR Letter	01/01/2012	Request to revise APSD acceptance criteria

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Amendment	1/2/2012	Commitment to explore alternative actuator designs to improve robustness
Amendment	1/6/2012	Revision of acceptance criteria for APSD

Reference ID: 3069082

7. NAME & ADDRESS OF APPLICANT:

Name:	Nycomed GmbH
Address:	Byk-Gulden-Strasse 2 78467 Konstanz Germany

NAME & ADDRESS OF AGENT:

Name:	Sunovion Pharmaceuticals Inc
Address:	84 Waterford Dr. Marlborough MA 01752
Representative:	Reneé M Carroll, MS, RAC, Senior Director, Regulatory Affairs
Telephone:	Telephone: (508) 357-7598 Fax: (508) 357-7491
E-mail	renee.carroll@sunovion.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Under review
b) Non-Proprietary Name (USAN): ciclesonide
c) Code Name/# BYK20426, B9207-015
d) Chem. Type/Submission Priority
- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Aerosol

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13. ROUTE OF ADMINISTRATION: Nasal Inhalation

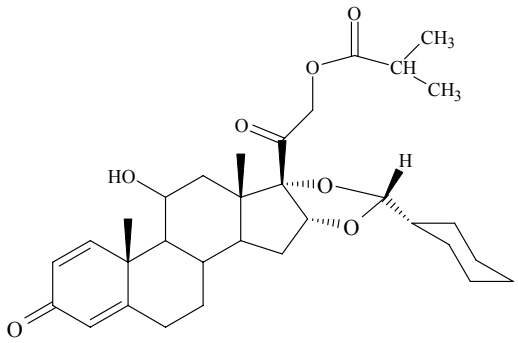
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(2'R)-2'Cyclohexyl-11b-hydroxy-21-isobutyryloxy-16b*H*-dioxolo[5',4':16,17]

Reference ID: 3069082

pregna-1,4-diene-3,20-dione



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Reference ID: 3069082

The Chemistry Review for NDA 202129

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I. Recommendations

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2. Drug Product
The drug product is a solution of ciclesonide in [redacted] (b) (4) dehydrated ethanol with HFA-134a (a non-CFC propellant) as the propellant. The solution is filled into an [redacted] (b) (4) canister to provide 30 or 60 actuations and sealed with a metering valve. A plastic actuator, which includes a dose counter, is included as part of the finished drug product. The valve is designed to deliver the drug accurately at 37 µg/actuation. (ex-actuator). The [redacted] (b) (4) canister and valve combination are exactly the same as those used in the approved drug product, Alvesco (ciclesonide) Inhalation Aerosol. The only difference is in the actuator, which is designed to deliver the drug to the nose.

The Pharmaceutical Development Report (PDR) supports the choice of ethanol content, the number of priming shots required (in the label), and the lack of a need for shaking prior to use [redacted] (b) (4)
The specifications include tests and acceptance criteria for ciclesonide content, alcohol content leak rate, valve delivery, impurities, Aerodynamic Particle Size Distribution (APSD) and delivered dose ex-actuator (Spray

Reference ID: 3069082

Content Uniformity =SCU).

The levels of most impurities are below (b) (4) and do not change on storage. The only impurity present on significant amounts (b) (4) has been qualified (b) (4)
The drug is stable, showing no trends over time for ciclesonide content, impurities, APDS or SCU.

The assembled inhaler includes the canister containing the drug product and the actuator, which has a dose counter built in. Drop tests show that a) the canister can be separated from the actuator and b) the does counter can give incorrect counts after dropping. Therefore the applicant was asked to commit to develop a new actuator which is more rugged.

The applicant has provided a Comparability Protocol to qualify future redesigns of the actuator. Changes that may impact actuator performance in terms of delivery of the drug will be filed as CBE30 and will include testing for APSD, SCU and other important parameters. Changes that may affect the dose indicator function will be submitted as CBE0 supplements and will include testing of count accuracy, drop testing and other parameters. Other changes that do not have the potential to affect either the actuator performance or the dose counter will be filed as Annual Reports. The Comparability protocol is acceptable.

The drug product is manufactured by (b) (4) This site is **ACCEPTABLE** in EES. The valve is manufactured by (b) (4) The actuator is manufactured by Aptar (b) (4)

B. Description of How the Drug Product is Intended to be Used
The proposed drug product label is for "treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older."

C. Basis for Approvability or Not-Approval Recommendation
The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach its target site in the nose consistently up to the labeled number of actuations on the label.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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Reference ID: 3069082

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/s/

ARTHUR B SHAW
01/09/2012

PRASAD PERI
01/09/2012
APSD specs are revised and a committment to improve the robistness of the drug product is provided. Recommend Approval.

NDA 202129

Tradename (ciclesonide) Nasal Aerosol (37 mcg/actuation)
Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Nycomed GmbH
Byk-Gulden Strasse 2
78467 Konstanz, Germany

Agent: Sunovian Pharmaceuticals Inc.
84 Waterford Dr.
Marlborough, MA 01752

Indication: Treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.
Dose: 1 actuation per nostril once daily (74 mcg/day).

Presentations: One strength but two fill presentations are proposed. Each canister contains 30 or 60 actuations.

EER Status: Recommendations: Acceptable
Consults: EA – Categorical exclusion provided
CDRH- N/A
Statistics – N/A
Methods Validation – Not recommended
DMETS- Acceptable
Biopharm– Acceptable
Microbiology – Adequate
Pharm/toxicology – Adequate

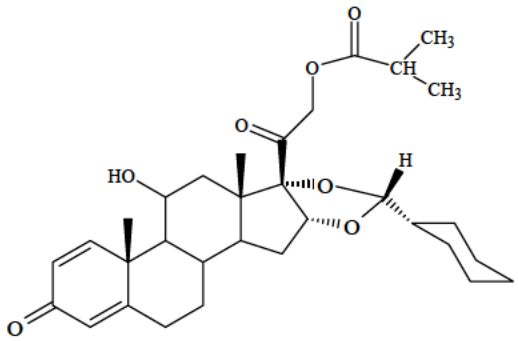
Original Submission: 19-Mar-2011

Post-Approval CMC Committment: To improve the robustness of the device. In drop studies, more than (b) (4) percent of the canisters separated from the actuators.

Background:
This is a standard NDA with a 10 month clock. The NDA is in electronic format with labeling provided in SPL format. A similar drug product Alvesco (ciclesonide) Inhalation Aerosol 80 mcg and 160 mcg (NDA 21658, approved 1/10/2008) and Omnaris (ciclesonide) Nasal Spray 50 mcg (NDA 22004, approved 10/20/2006) have been approved by the Agency recently.

Drug Substance:
The drug substance is a corticosteroid and is a white to yellowish powder. It is freely soluble in ethanol, insoluble in water, and soluble in ethanol. It is synthesized (b) (4) yielding the R-epimer. The chemical name is (2'R)-2'Cyclohexyl-11b-hydroxy-21-isobutyryloxy-

16bH-dioxolo[5',4':16,17] pregna-1,4-diene-3,20-dione. The molecular formula is $C_{32}H_{44}O_7$ and the molecular weight is 540.69.



The complete CMC information is contained in DMF [redacted] (b) (4), which has been recently updated, reviewed and found acceptable. It is manufactured by [redacted] (b) (4) This site was found ACCEPTABLE in the EER.

The drug substance is controlled by testing for Identity (IR, Color, [redacted] (b) (4)), Specific Rotation, Acidity, Water Content, Residue on Description (appearance), Melting Point, Particle Size, Identity (IR and HPLC), Water content, Sulfated Ash, Heavy metals, Appearance of solution (Clarity and Color), Microbial purity, Residual Solvents, Ethanol, Specific Rotation, related Substances, Assay, Ignition, [redacted] (b) (4) Limit of Foreign Alkaloids, Residual Solvents, and Assay.

A retest period of [redacted] (b) (4) months is proposed by the manufacturer of the drug substance.

Conclusion: The drug substance is satisfactory.

Drug Product:

The drug product is a solution of ciclesonide in [redacted] (b) (4) dehydrated ethanol with HFA-134a (a non-CFC propellant) as the propellant. The solution is filled into an [redacted] (b) (4) canister to provide 30 or 60 actuations and sealed with a metering valve. A plastic actuator, which includes a dose counter, is included as part of the finished drug product. The valve is designed to deliver the drug accurately at 37 µg/actuation. (ex-actuator). The [redacted] (b) (4) canister and valve combination are exactly the same as those used in the approved drug product, Alvesco (ciclesonide) Inhalation Aerosol. The only difference is in the actuator, which is designed to deliver the drug to the nose.

The drug product is manufactured by [redacted] (b) (4). This site is **ACCEPTABLE** in EES. The valve is manufactured by [redacted] (b) (4) The actuator is manufactured by Aptar [redacted] (b) (4)

The applicant changed the design of the actuator [redacted] (b) (4) The original version of the actuator is "V1" and the new version is "V2." A number of other changes were made [redacted] (b) (4) Since all of these changes were done after the pivotal clinical trials, the applicant provided an in vitro study to demonstrate the equivalence of the two actuators in terms of PSD and SCU.

[redacted] (b) (4)

Reference ID: 3064578

(b) (4)

No performance differences are seen in the *in vitro* data for the two actuators. A statistical analysis conducted by the applicant and an independent analysis conducted by FDA (review by Meiyu Shen (Biometrics) on December 6, 2011) found that the two actuators were equivalent.

The drug product is controlled by testing for Appearance, Identification, Microbial Analysis, (b) (4) Ethanol content, Fill weight, Assay, Impurities, Spray Content Uniformity, Aerodynamic Particle Size Distribution, Foreign particulate Matter, Leak Rate, Valve Delivery, Number of Actuations, and Leachables.

The applicant has proposed (b) (4) APSD specifications (b) (4) While the limits are acceptable, it is not clear if there are any failures (b) (4) especially since the drug product is a solution. The applicant is being asked to provide data to justify (b) (4) testing or revise the criteria (b) (4)

The applicant has provided a comparability protocol to propose changes to the actuator and to report the changes to the Agency based on risk. For (b) (4) changes to the actuator (b) (4), the applicant has proposed (b) (4) Since this is a solution formulation for a nasal aerosol, this is acceptable.

Note that the valves for the two devices: Alvesco Inhalation Aerosol and ciclesonide nasal aerosol are identical. There is more drug retained in the actuator for the nasal aerosol per actuation even though the orifice diameter is larger (0.50 mm for nasal actuator compared to 0.30 mm for inhalation actuator). (b) (4)

The applicant has proposed an expiration data of 24 months for the 60 actuation fill and 18 months for the 30 actuation fill. These are Acceptable.

Conclusion: The drug product is acceptable **pending the commitment and revision to APSD specification**s.

CMC issues that are still pending:
Post approval commitment to improve the robustness of the product, revision to drug product APSD specifications to justify (b) (4) testing.

Overall Conclusion: The NDA is recommended for **approvable action** from CMC standpoint pending committing to improve the device robustness so that the separation between the actuator and canister is rectified when dropped and to revise the APSD specifications as appropriate.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

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/s/

PRASAD PERI

12/28/2011

Approvable action till commitment is received and justification for APSD specification is provided.

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R REGIONAL INFORMATION 151

II. Review of Common Technical Document-Quality (CTD-Q) Module 1 155

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B. Environmental Assessment or Claim of Categorical Exclusion 155

Reference ID: 3063735

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3063735

Chemistry Review Data Sheet

1. NDA 202129

2. REVIEW #:1

3. REVIEW DATE: December 23, 2011

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Original	03/19/2011	None
IR via e-mail	07/11/2011	Request SAS data set supporting comparison between V1 and V2 actuators.
Amendment	07/22/2011	Response to 7/11/2011 IR Letter
IR via e-mail	10/04/2011	Request BE profile comparison and SAS datasets supporting comparison between V1 and V2 actuators.
Amendment BC	10/21/2011	Response to 10/21/2011 IR Letter

Reference ID: 3063735

7. NAME & ADDRESS OF APPLICANT:

Name:	Nycomed GmbH
Address:	Byk-Gulden-Strasse 2 78467 Konstanz Germany

NAME & ADDRESS OF AGENT:

Name:	Sunovion Pharmaceuticals Inc
Address:	84 Waterford Dr. Marlborough MA 01752
Representative:	Reneé M Carroll, MS, RAC, Senior Director, Regulatory Affairs
Telephone:	Telephone: (508) 357-7598 Fax: (508) 357-7491
E-mail	renee.carroll@sunovion.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Under review
b) Non-Proprietary Name (USAN): ciclesonide
c) Code Name/# BYK20426, B9207-015
d) Chem. Type/Submission Priority
- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Aerosol

12. STRENGTH/POTENCY: 37 µg/actuation (ex-actuator)

(b) (4)

13. ROUTE OF ADMINISTRATION: Nasal Inhalation

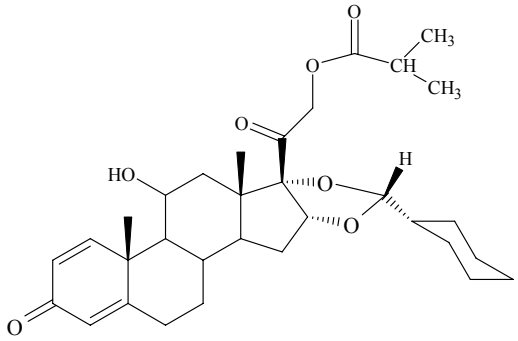
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(2'R)-2'Cyclohexyl-11b-hydroxy-21-isobutyryloxy-16b*H*-dioxolo[5',4':16,17]

Reference ID: 3063735

pregna-1,4-diene-3,20-dione



$C_{32}H_{44}O_7$. 540.69

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	II		(b) (4)	Adequate	11/18/2009 No significant changes since last review
	IV			Adequate	04-May-2004 No significant changes since last review
	V			Adequate	12/02/2011
	III			Adequate	12/02/2011
	III			Adequate	24-May-2004 No significant changes since last review
	III			Adequate	08/23/2011

Reference ID: 3063735

(b) (4)		(b) (4)		
	III		Adequate	05-Oct -2004 No significant changes since last review
	II		Adequate	07-Jul-2004 No significant changes since last review
	III		Adequate	03/02/2006 No significant changes since last review
	III		Adequate	No review necessary not product contact.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,391	Ciclesonide MDI
NDA	19658	Alvesco (ciclesonide) Inhalation Aerosol

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	**ACCEPTABLE**	12/06/2011	Meiyu Shen
EES	Acceptable	22-Apr-2011	N/A
Methods Validation	Not submitted		
DMETS	Proprietary name	Under review	
EA	N/A		
Microbiology	**ACCEPTABLE** for NDA 21658	04-Apr-2004	Bryan Riley

Reference ID: 3063735

The Chemistry Review for NDA 202129

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable pending receipt of the post-approval commitment to develop a more rugged actuator/dose counter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

The applicant has been requested to commit to developing a more rugged actuator/dose counter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is a corticosteroid and is a white to yellowish powder. It is freely soluble in ethanol, insoluble in water, and soluble in ethanol. It is synthesized [redacted] (b) (4) yielding the R-epimer. The complete CMC information is contained in DMF [redacted] (b) (4), which has been recently updated, reviewed and found acceptable. It is manufactured by [redacted] (b) (4) This site was found **ACCEPTABLE** in the EER.

2. Drug Product

The drug product is a solution of ciclesonide in [redacted] (b) (4) dehydrated ethanol with HFA-134a (a non-CFC propellant) as the propellant. The solution is filled into an [redacted] (b) (4) canister to provide 30 or 60 actuations and sealed with a metering valve. A plastic actuator, which includes a dose counter, is included as part of the finished drug product. The valve is designed to deliver the drug accurately at 37 µg/actuation. (ex-actuator). The [redacted] (b) (4) canister and valve combination are exactly the same as those used in the approved drug product, Alvesco (ciclesonide) Inhalation Aerosol. The only difference is in the actuator, which is designed to deliver the drug to the nose.

The Pharmaceutical Development Report (PDR) supports the choice of ethanol content, the number of priming shots required (in the label), and the lack of a need for shaking prior to use [redacted] (b) (4)
The specifications include tests and acceptance criteria for ciclesonide

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content, alcohol content leak rate, valve delivery, impurities, Aerodynamic Particle Size Distribution (APSD) and delivered dose ex-actuator (Spray Content Uniformity =SCU).

The levels of most impurities are below (b) (4) and do not change on storage. The only impurity present on significant amounts (b) (4) has been qualified (b) (4)
The drug is stable, showing no trends over time for ciclesonide content, impurities, APDS or SCU.

The assembled inhaler includes the canister containing the drug product and the actuator, which has a dose counter built in. Drop tests show that a) the canister can be separated from the actuator and b) the does counter can give incorrect counts after dropping. Therefore the applicant was asked to commit to develop a new actuator which is more rugged.

The applicant has provided a Comparability Protocol to qualify future redesigns of the actuator. Changes that may impact actuator performance in terms of delivery of the drug will be filed as CBE30 and will include testing for APSD, SCU and other important parameters. Changes that may affect the dose indicator function will be submitted as CBE0 supplements and will include testing of count accuracy, drop testing and other parameters. Other changes that do not have the potential to affect either the actuator performance or the dose counter will be filed as Annual Reports. The Comparability protocol is acceptable.

The drug product is manufactured by (b) (4) This site is **ACCEPTABLE** in EES. The valve is manufactured by (b) (4) The actuator is manufactured by Aptar (b) (4)

B. Description of How the Drug Product is Intended to be Used

The proposed drug product label is for "treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older."
The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach its target site in the nose consistently up to the labeled number of actuations on the label.

C. Basis for Approvability or Not-Approval Recommendation

The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach its target site in the nose consistently up to the labeled number of actuations on the label.

III. Administrative

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A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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Reference ID: 3063735

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/s/

ARTHUR B SHAW
12/23/2011

PRASAD PERI
12/23/2011

ONDQA Review for
OND Division of Pulmonary Allergy and Rheumatology Products
Initial Quality Assessment and Filing Review
Date: May 4, 2011

NDA: 202129
Product Name: Ciclesonide Nasal Aerosol
Applicant: Nycomed GmbH, Konstanz, Germany (Agent: Sunovion Pharmaceuticals Inc.)
Letter Date: 3/18/2011
Stamp Date: 3/21/11
PDUFA Date: 1/21/2012
ONDQA 5 month date: 8/21/11
Proposed Proprietary Name: (b) (4)
Established Name: ciclesonide nasal aerosol
Dosage form and strength: nasal aerosol, 37 mcg delivered per actuation, ex-actuator
Route of Administration: nasal
Indications: treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older.
CMC Lead (acting): Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA
Filability recommendation: Fileable.
Review team recommendation: Single primary reviewer (Arthur Shaw, Ph.D.)
Regulatory Briefing Recommendation: Branch level
Time goals:

- Initial Quality Assessment in DFS: 5/5/11
- Filing decision "Day 45": 5/5/11
- Filing review issues "Day 74": 6/3/11
- **Chemistry Review (DR/IR) letter:** by 8/21/11
- Mid-cycle meeting "Month 5":
- Wrap Up:
- **Final Chemistry Review "Month 8" in DFS:** 11/21/11
- PDUFA: 1/21/2012

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	N.A.
CDRH	To be requested for human factors evaluation
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 4/18/2011. Compliance has found the facilities to be acceptable on 4/22/2011.
DMETS	Labeling consult request will be sent as part of DPARP's request.
Methods Validation	Methods validation for non-compendial methods may be requested of FDA laboratories if deemed necessary by the reviewer after test methods are finalized.
Microbiology	To be requested (for data on microbial challenge test and

CONSULTS/ CMC RELATED REVIEWS	COMMENT
	microbial analysis)
Pharm/Tox	DS and DP impurities/degradants/leachables/foreign particulates should be evaluated for safety, as necessary (b) (4)

Notes:

Background:

The following information on intended use is taken from Module 2.2:

> "This NDA is being submitted to support the safety and efficacy of a pressurized hydrofluoroalkane (HFA) aerosolized formulation of ciclesonide administered via a metered dose nasal aerosol with a nasal actuator for the treatment of symptoms associated with allergic rhinitis (resulting from seasonal and perennial allergens) in adolescents and adults 12 years of age and older. The proposed dosage strength is a once daily total dose of 80 mcg administered as 1 actuation (40 mcg) per nostril via nasal actuator."

The following information on development is taken from Module 2.3.

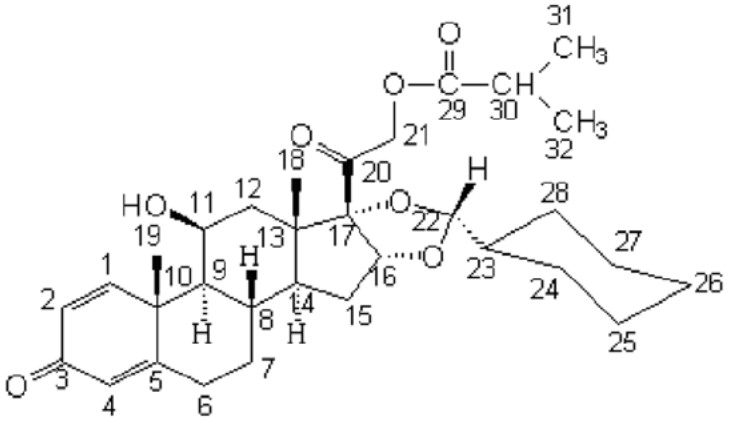
> "Clinical studies evaluating the ciclesonide nasal aerosol formulation for the treatment of allergic rhinitis were performed under IND 74674, which was originally submitted by Altana Pharma US, Inc., a subsidiary of Nycomed GmbH on 10 November 2006. On 25 January 2008, Sepracor Inc., now known as Sunovion Pharmaceuticals Inc. (Sunovion) entered into a licensing agreement with Nycomed to develop and market ciclesonide products in the United States. Nycomed appointed Sunovion as their US agent for IND 74674 on 12 May 2008. Nycomed transferred ownership of this IND to Sunovion on 23 July 2008. As sponsor of IND 74674, Sunovion conducted additional clinical studies, including the pivotal Phase 3 studies in subjects with SAR and PAR. While Sunovion is the current Sponsor of this IND, the applicant for the ciclesonide nasal aerosol NDA is Nycomed."

The following introductory CMC information is taken from Module 2.3.1:

> "Nycomed GmbH is seeking approval for Ciclesonide (b) (4) Nasal Aerosol (30 and 60 actuations) 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. The active component for Ciclesonide Nasal Aerosol is ciclesonide, a non-halogenated, anti-inflammatory glucocorticoid having the chemical name pregna-1,4-diene-3,20-dione,16,17-[[(R)-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,(11b,16a),with a molecular formula of $C_{32}H_{44}O_7$ and molecular weight of

540.7g/mol. Ciclesonide is cleaved at carbon position 21 (C21) by intracellular esterases in the respiratory tract to form a biologically active metabolite (RM1, B9207-021) with 120-fold greater affinity for the glucocorticoid receptor than the parent compound. The R-epimer of racemic ciclesonide was selected for development [redacted] (b) (4) Ciclesonide Nasal Aerosol is a solution formulation of Ciclesonide with [redacted] (b) (4) Dehydrated Alcohol, USP and [redacted] (b) (4) HFA 134a (1,1,1,2 tetrafluoroethane) propellant, contained within a [redacted] (b) (4) canister and delivered via the dose-indicating nasal actuator. The product strength proposed for marketing, (Ciclesonide [redacted] (b) (4) Nasal Aerosol), delivers 50mcg of Ciclesonide per actuation (ex-valve),and yields a delivered dose (ex-actuator) of 37mcg per actuation. Ciclesonide Nasal Aerosols are available in two pack sizes, delivering a minimum of 30 or 60 actuations." Note that the approved Alvesco (ciclesonide) Inhalation Aerosol also uses a [redacted] (b) (4) canister.

Drug substance



$C_{32}H_{44}O_7$ 540.7 g/mol

CMC information pertaining to ciclesonide drug substance is referenced to DMF [redacted] (b) (4) The applicant has mainly provided drug substance specifications including validated analytical methods in the NDA.

Nycomed drug substance specifications for the unmicronized drug substance are listed below. These specifications are said to be based on those in DMF [redacted] (b) (4).

Test parameter	Specification	Analytical method
PHYSICOCHEMICAL PROPERTIES		
Description:	white to yellow-white [redacted] (b) (4) powder	Version 4 (SAS01E.002033QU)
Melting point (DSC):	207 – 211°C	Version 3 (SAS01E.000721QU)
Particle size (laser diffraction)*:	[redacted] (b) (4)	Version 1 (SAS01E.002034QU)
IDENTITY		
IR spectrum:	corresponds to reference	Version 2 (SAS01E.002035QU)
HPLC:	corresponds to reference	Version 15 (SAS01E.002006QU)
PURITY		
Water:	[redacted] (b) (4)	Version 4 (SAS01E.001869QU)
Sulfated ash:		Version 1 (SAS01E.002036QU)
Heavy metals:		Version 6 (SAS01E.001418QU)
Appearance of solution: - Clarity - Coloration	clear [redacted] (b) (4)	Version 3 (SAS01E.002038QU)

Test parameter	Specification	Analytical method
Microbiological testing: - TAMC - Bile-tolerant gram-negative bacteria - Staphylococcus aureus - Pseudomonas aeruginosa	(b) (4)	Ph.Eur.2.6.12 Ph.Eur.2.6.13
(b) (4)		Version 12 (SAS01E.001225QU)
Specific rotation:		Version 2 (SAS01E.002037QU)
Related substances (HPLC): (b) (4) - Unknown impurities, largest single value - Total impurities, unknown - Total impurities (known + unknown)		Version 15 (SAS01E.002006QU)
CONTENT		
HPLC:		Version 15 (SAS01E.002006QU)

Analytical Procedures – descriptions of Nycomed analytical procedures are provided and are indicated to be based on those of (b) (4) DMF (b) (4). The following information pertaining to the validated methods is from Module 2.3.S.4.2: "The physical/chemical and microbiological tests are carried out in accordance with Ph.Eur. The identity/purity test and assay is carried out by an (b) (4) HPLC method (b) (4) This method is capable of detecting all potential and actual impurities. The assay and quantitation of the specified known impurities is carried out with the aid of corresponding reference substances. Unknown impurities are calculated (b) (4) "

Note that Table 1, Section 3.2.S.4.2, pertaining to Analytical Procedures, doesn't contain a hyperlink to the methods for Related Substances (HPLC) and Content (HPLC), but they are accessed through the link for the method for ID (HPLC).

Batch data are provided for a number of batches used in clinical, toxicological, stability and process validation studies.

Comment: The applicant has specifications and tests for accepting the drug substance. DMF (b) (4) for ciclesonide drug substance had been found adequate to support Alvesco (ciclesonide) Inhalation Aerosol on 12/21/2007. Subsequent submissions dated 9/25/2009 and 5/10/2010 were reviewed and found adequate in an NAI review dated 3/28/2011.

Drug product

The following information is from Module 2.3.1.

Table 1: Summary of the Nomenclature Used for Ciclesonide Nasal Aerosol

Concentration (mg/mL)	ex-actuator delivery (mcg/actuation)	ex-valve delivery (mcg/actuation)	Concentration (% w/w)
1	37	50	(b) (4)

The composition of Ciclesonide (b) (4) Nasal Aerosols is presented in Table 2.

Table 2: Composition of Ciclesonide 1mg/mL Nasal Aerosols

Name of Ingredient	Quantity				Function	References to Specifications
	% w/w	g per filled canister[a]		mg per actuation (ex-valve)		
		30 Actuation	60 Actuation			
Active Ingredient						
Ciclesonide	(b) (4)			0.050[b]	Corticosteroid	3.2.S.4.1 Specifications
Other Ingredients						
Dehydrated Alcohol, USP	(b) (4)				(b) (4)	3.2.P.4.1 Specifications
HFA-134a					Propellant	3.2.P.4.1 Specifications
Total Quantity						

[a] This is based on a target fill weight of 4.7g or 6.1g respectively for the 30 and 60 actuation products.
[b] This equates to 37mcg per actuation ex-actuator.

Note that there are two proposed presentations of the drug product: fills of 30 actuations and 60 actuations. The container closure system consists of a nominal [redacted] (b) (4) canister [redacted] (b) (4), a 50 mcL metering valve [redacted] (b) (4) and a nasal actuator with an integrated actuation counter. The Aptar Pharma (formerly Valois) actuator is illustrated later in this review (from the NDA, Module 2.3.P.2.5.5.1).

Pharmaceutical development information is provided, which includes basic information about the formulation development and a number of characterization studies. The following information is provided from Module 2.3.P.2.1.1.

> "Ciclesonide HFA Products are formulated as solution products. [redacted] (b) (4) A formulation of [redacted] (b) (4) dehydrated alcohol and [redacted] (b) (4) HFA-134a was selected...
>
> As agreed in the FDA End of Phase 2 meeting (correspondence fax dated January 9th 2008) for Ciclesonide Nasal Aerosols, IND 74674 the studies supporting the development of the formulation and characterization of filled canisters [redacted] (b) (4) significant portions of the pharmaceutical development sections convey these existing data."

[redacted] (b) (4)

Data pertaining to toxicological, clinical and stability batches during drug development are provided in a table.

The pharmaceutical development section contains the results of drug product characterization studies, including the following (as examples): in-vitro dose proportionality, comparative stability data for 30, 60 [redacted] (b) (4) actuation pack sizes, tail off characteristics, effect of [redacted] (b) (4) content on performance, temperature cycling, and a simulated shipping study. Priming/re-priming, cleaning, leak rate, microbial challenge, nosepiece retention, spray pattern, and plume geometry were evaluated. The placebo was studied for leachables and a correlation between container closure component extractables and placebo leachables was established: reference is made to DMF [redacted] (b) (4) and DMF [redacted] (b) (4) [redacted] has conducted a toxicological evaluation of leachables: see DMF [redacted] (b) (4) Leachables that were observed (storage time is not indicated – see [redacted] (b) (4) DMF for details) were present [redacted] (b) (4) for all but one leachable [redacted] (b) (4) This should be evaluated for safety by the non-clinical reviewer [redacted] (b) (4)

Critical manufacturing process parameters which are defined include residence time, heat stress, and equilibration time (per Module 2.3.P.2.4.1).

The actuator requires three priming actuations initially, and repriming after 10 days of non use.

The container closure system is made up of the 50 mcL metering valve, (b) (4) an (b) (4) canister (b) (4), and the actuator. However, the (b) (4) canister is to be used with the 30 and 60 actuation presentations (to-be-marketed) (b) (4)

The actuator (see figure later in this review) was developed by Aptar Pharma (formerly Valois), and it contains an integrated dose indicator. The initial actuator version (Version 1, or V1) was used in the clinical and stability studies. Manufacturing problems required that this version be modified (to Version 2 or V2) (b) (4) An actuator comparability study was conducted and the differences "are not considered pharmaceutically significant" by the applicant.

Actuator development included studies of spray pattern and plume geometry (b) (4) Stability of actuators was evaluated up to 21 months at 25°C/60%RH and robustness was demonstrated according to the applicant. Actuator extractables were evaluated as potential leachables in the drug product and they were not found in the product (it isn't clear in the NDA QOS if the applicant was looking for migration of actuator extractables into the formulation inside the canister, but that is implied). Other characterization tests conducted with the actuator include the following: dose indicator count accuracy, actuator drop test, force to count and force to expel. A patient in-use study was conducted to evaluate the counter.

The applicant has provided the following image of the plume from the proposed drug product:

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/s/

ALAN C SCHROEDER
05/05/2011
CMC Recommendation: NDA is fileable.

PRASAD PERI
05/05/2011
I concur

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202129/000	**Sponsor:**	NYCOMED GMBH
Org Code:	570		84 WATERFORD DR
/:	3		MARLBOROUGH, MA 017527010
Stamp Date:	21-MAR-2011	**Brand Name:**	Ciclesonide
PDUFA Date:	21-JAN-2012	**Estab. Name:**	
Action Goal:		**Generic Name:**	Ciclesonide
District Goal:	22-NOV-2011	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; AEROSOL; CICLESONIDE; 37MCG	

FDA Contacts:	S. PATWARDHAN	Project Manager	(HF-01)	301-796-4085
	A. SHAW	Review Chemist		301-796-1460
	A. SCHROEDER	Team Leader		301-796-1749

Overall Recommendation: ACCEPTABLE on 22-APR-2011 by D. SMITH ()

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: (b) (4)

Profile: **OAI Status:** NONE

lestone: OC RECOMMENDATION

Milestone Date: 22-APR-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-APR-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Reference ID: 3077685

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9611622 **FEI:** 3002806542		
	NYCOMED GMBH (FRMLY: ALTANA) ROBERT BOSCH STRASSE 8		
	SINGEN (HOHENTWIEL), , GERMANY		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-APR-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Reference ID: 3077685

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/s/

NIKOO N MANOCHEHRI KALANTARI
01/26/2012