CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-004

CHEMISTRY REVIEW(S)

Chemistry Review Cover Sheet

NDA 22-004
Omnaris (ciclesonide) Nasal Spray
Arthur B. Shaw, Ph.D.
ONDQA/DPA1

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-004

2. REVIEW #3

3. REVIEW DATE: September 28, 2006

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

5. PREVIOUS DOCUMENTS:

Submissions Reviewed	Applicant's Submission Number	Document Date	Comment
Original	0000	21-Dec-2005	Filing Review Complete March 20, 2006
Amendment BC	0001	02-Mar-2006	Response to telephone inquiries regarding [redacted] composition (Feb 10, 2006) and status of manufacturing sites (Feb 21, 2006)
Amendment BC	0004	24-Mar-2006	Partial response to IR letter Mar 17, 2006
Amendment BC	0007	14-Apr-2006	Remainder of response to IR letter
Amendment BC	0008	21-Apr-2006	Partial stability update
Amendment BC	0010	02-Jun-2006	Updated stability, Executed Batch Record, response to IR for [redacted]
Amendment BC	0014	21-Jul-2006	New specs for [redacted]
Amendment BC	0015	02Aug-2006	SAS stability tables for [redacted]
Amendment BC	0017	10-Aug-2006	[redacted]
Amendment BC	0018	11-Aug-2006	Response to DR Letter #1
Amendment BC	0019	14-Aug-2006	Proposed trade name
Amendment BC	0020	17-Aug-2006	[redacted]
Amendment BC	0021	18-Aug-2006	[redacted]
Amendment BC	0022	21-Aug-2006	Methods Validation for new [redacted] method

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Applicant's Submission Number	Document Date	Comment
Amendment BC	0024	29-Aug-2006	Commitments to revise specs and stability protocol
Amendment BC	0026	15-Sep-2006	Response to 06-Sep-2006 DR Letter #2
Amendment BC	0029	26-Sep-2006	Response to fax info request22-Sep-2006

FDA Documents	Document Date	Comment
Chemist's Filing Memo	20-Mar-2006	Acceptable for filing. Additional info requested
Addendum to Filing Memo	20-Mar-2006	
IR Letter	17-Mar-2006	Info request from Filing memos
Review #1	25-Jul-2006	Comments
DR Letter #1	27-Jul-2006	Comments
Chem Review #2	29-Aug-2006	Comments
DR Letter #2	06-Sep-2006	Propose new [redacted] stability spec and out-of pouch storage time
CMC IR fax	22-Sep-2006	Request for info on stability protocol and weight loss test.

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Pharma, Inc.
Address:	2020 Park Avenue
	Florham Park NJ 07932-0890
Representative:	George Chen
Telephone:	973 514-4240

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Omnaris
b) Non-Proprietary Name (USAN): ciclesonide
c) Code Names:: BYK20426, B9207-015
d) Chem. Type/Submission Priority
   - Chem. Type: 1
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Nasal spray

12. STRENGTH/POTENCY: 50 µg

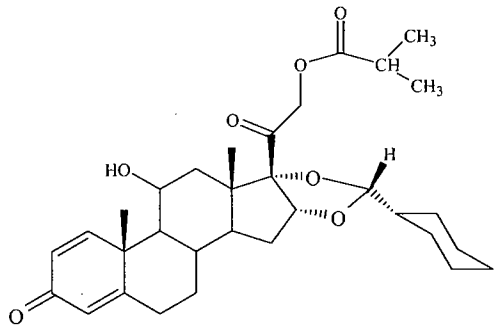
13. ROUTE OF ADMINISTRATION: Intranasal

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



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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
Reviewed

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED
[redacted]	II	[redacted]	Ciclesonide [redacted]	Adequate	31-Jul-2006
[redacted]	II	[redacted]	Ciclesonide [redacted] = drug substance	Adequate	29-Aug-2006
[redacted]	II	[redacted]	[redacted]	Adequate	29-Aug-2006
[redacted]	III	[redacted]	[redacted]	Adequate	29-Aug-2006 IR Letter 31-Aug-2006
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	III	[redacted]	[redacted]	Adequate	31-Jul-2006
[redacted]	III	[redacted]	[redacted]	Adequate	31-Jul-2006 IR Letter 02-Aug-2006
[redacted]	III	[redacted]	[redacted]	Adequate	14-Aug-2006
[redacted]	III	[redacted]	[redacted]	Adequate	27-Jul-2006 IR Letter 31-Jul-2006
[redacted]	III	[redacted]	[redacted]	Adequate	14-Aug-2006
[redacted]	III	[redacted]	[redacted]	Adequate	31-Jul-2006
[redacted]	III	[redacted]	[redacted]	Adequate	31-Jul-2006

DMFs Not reviewed

DMF #	TYPE	HOLDER	ITEM REFERENCED	Reason for no review
	III			
	III			
	III			Not in product contact

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	LOA Date
IND	65,488	Ciclesonide nasal spray	Not necessary held by Altana

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	24 month expiration date acceptable	01-Sep-2006	Roswitha Kelly
Pharm/Tox	Acceptable for leachables	30-Jun-2006	Huiqing Hao
	Acceptable for increased levels of	23-Aug-2006	Huiqing Hao
Methods Validation	Request sent	15-Aug-2006	Pending
DMETS	Proprietary name under review	28-Aug-2006	Pending
EA	Categorical exclusion granted	N/A	N/A
Microbiology	Acceptable for EES	23-Aug-2006	Bryan Riley
	Acceptable	03-Feb-2006	Profile
	Acceptable	17-Feb-2006	District File Review
	Acceptable	03-Feb-2006	Profile
	Acceptable	08-Feb-2006	District File Review
	Acceptable	21-Aug-2006	Inspection
Altana Pharma (drug product manufacturing)	Assigned to IB	08-Feb-2006	Pending
	Assigned to IB	08-Feb-2006	Pending

The Chemistry Review for NDA 22004

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The application is recommended for approval in terms of Chemistry, Manufacturing, and Controls with an "in-pouch" expiration date of 24 months and a recommended "in-use" storage time of no more than 4 months.. Two inspections are pending. See discussion below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.
None

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 [redacted] It is synthesized from [redacted]

For the nasal spray formulation, the drug substance is [redacted]

2. Drug Product
The drug product is a hypotonic aqueous suspension, with 120 puff/bottle (commercial) [redacted] presentations and is filled into a [redacted] glass bottle. The drug substance is insoluble in the formulation and is present as fine particles in suspension. The formulation contains microcrystalline cellulose and carboxymethylcellulose sodium NF (MCC/CMC Na) [redacted] and potassium sorbate/sodium edetate [redacted] The pH is adjusted to [redacted]

The bottle has a plastic outer sleeve to protect against breakage. A plastic pump (with a plastic cap) , which meters the dose, is attached. The whole bottle-pump assembly is packed in an aluminum foil pouch with an oxygen absorber, [redacted] Testing for [redacted] leachables is controlled by extractables testing [redacted] Testing for [redacted] and [redacted] is done on the drug product. See discussion below concerning [redacted] levels.

The pharmaceutical development report (PDR) supports the formulation, the number of priming shots required (in the label), the need for shaking prior to use (in the label) and the following drug delivery characteristics: pump delivery (PD), spray content uniformity (SCU), droplet size distribution (DSD), spray pattern (SP) and particle size distribution (PSD).. The PD ensures that the same volume of drug product is delivered with each spray and the SCU ensures that the same amount of drug is delivered with each spray. The SCU is the basis for the labeled strength of the drug (50 µg). The DSD and the SP ensure that the distribution of the drug in the nasal passages is consistent and reaches the target organ. The PSD does not affect the distribution of the drug in the respiratory system (unlike a metered dose inhaler). The PSD is expected to have minimal impact on the distribution of the drug in the nasal passages and no effect has been demonstrated on drug absorption.

The levels of most impurities are below [redacted] and do not change on storage. The only [redacted] present on significant amounts is the [redacted] which is a process-related impurity. It has been qualified at [redacted] in the review of [redacted] for ciclesonide metered dose inhaler, which is cross-referenced in a letter dated April 20, 2005.

The applicant submitted [redacted] months of stability data on August 10, 2006 for batches manufactured at [redacted] scale to be used as the primary stability data to support the expiration date. They also submitted stability data on that date for batches manufactured at the propose commercial scale of [redacted]. The [redacted] stability data support requested expiration date of 24 months for all parameters except the

[redacted]

[redacted]

The inspection for the site for finished dosage form manufacture is pending and is expected to be completed the week of October 22, 2006. The inspection for the site for [redacted] pending and may not be completed in time for the PDUFA fate. This process does not involve any synthetic steps or steps that could increase microbiological contamination. Therefore a satisfactory inspection of this site is not necessary for approval of the application.

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

According to the proposed label, the drug product is "indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic in adults and children years of age and older." [redacted]

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 Signed off in DFS

27 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- S

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/s/

Arthur B. Shaw
9/28/2006 07:25:34 PM
CHEMIST
CMC Aprpoval Inspection pending

Blair Fraser
9/29/2006 05:25:26 AM
CHEMIST

Chemistry Review Cover Sheet

NDA 22-004
Omnaris (ciclesonide) Nasal Spray
Arthur B. Shaw, Ph.D.
ONDQA/DPA1

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. NDA 22-004

2. REVIEW #2

3. REVIEW DATE: August 29, 2006

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

5. PREVIOUS DOCUMENTS:

Submissions Reviewed	Applicant's Submission Number	Document Date	Comment
Original	0000	21-Dec-2005	Filing Review Complete March 20, 2006
Amendment BC	0001	02-Mar-2006	Response to telephone inquiries regarding [redacted] composition (Feb 10, 2006) and status of manufacturing sites (Feb 21, 2006)
Amendment BC	0004	24-Mar-2006	Partial response to IR letter Mar 17, 2006
Amendment BC	0007	14-Apr-2006	Remainder of response to IR letter
Amendment BC	0008	21-Apr-2006	Partial stability update
Amendment BC	0010	02-Jun-2006	Updated stability, Executed Batch Record, response to IR for [redacted]

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Applicant's Submission Number	Document Date	Comment
Amendment BC	0014	21-Jul-2006	New specs for [redacted]
Amendment BC	0015	02Aug-2006	SAS stability tables for [redacted]
Amendment BC	0017	10-Aug-2006	[redacted]
Amendment BC	0018	11-Aug-2006	Response to DR Letter
Amendment BC	0019	14-Aug-2006	Proposed trade name
Amendment BC	0020	17-Aug-2006	[redacted]
Amendment BC	0021	18-Aug-2006	[redacted]
Amendment BC	0022	21-Aug-2006	Methods Validation for new [redacted] method

FDA Documents	Document Date	Comment

Chemist's Filing Memo	20-Mar-2006	Acceptable for filing. Additional info requested
Addendum to Filing Memo	20-Mar-2006	
IR Letter	17-Mar-2006	Info request from Filing memos
Review #1	25-Jul-2006	Comments
Discipline Review Letter	27-Jul-2006	Comments

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Pharma, Inc.
Address:	2020 Park Avenue
	Florham Park NJ 07932-0890
Representative:	George Chen
Telephone:	973 514-4240

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Omnaris
b) Non-Proprietary Name (USAN): ciclesonide
c) Code Names:: BYK20426, B9207-015
d) Chem. Type/Submission Priority
   - Chem. Type: 1
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Nasal spray

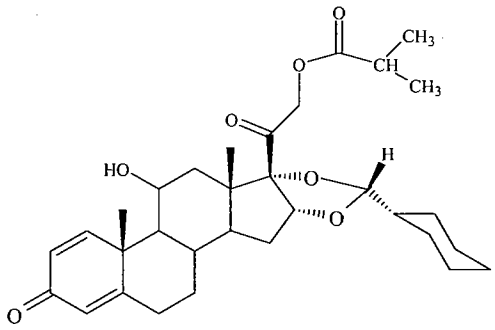
12. STRENGTH/POTENCY: 50 µg

13. ROUTE OF ADMINISTRATION: Intranasal

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



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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Reviewed

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED
	II		Ciclesonide [redacted]	Adequate	31-Jul-2006
	II		Ciclesonide [redacted] = drug substance	Adequate	29-Aug-2006
	II			Adequate	29-Aug-2006
	III			Adequate	29-Aug-2006
	III			Adequate	31-Jul-2006
	III			Adequate	31-Jul-2006 IR Letter 02-Aug-2006
	III			Adequate	14-Aug-2006
	III			Adequate	27-Jul-2006 IR Letter 31-Jul-2006
	III			Adequate	14-Aug-2006
	III			Adequate	31-Jul-2006
	III			Adequate	31-Jul-2006

DMFs Not reviewed

DMF #	TYPE	HOLDER	ITEM REFERENCED	Reason for no review
[redacted]	III	[redacted]	[redacted]	[redacted]
	III			
	III			Not in product contact

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	LOA Date
[redacted]			
IND	65,488	Ciclesonide nasal spray	Not necessary held by Altana

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	24 month expiration date acceptable	Draft 28-Aug-2006	Roswitha Kelly
Pharm/Tox	Acceptable for leachables	30-Jun-2006	Huiqing Hao
	Acceptable for increased levels of [redacted]	23-Aug-2006	Huiqing Hao
Methods Validation	Request sent	15-Aug-2006	Pending
DMETS	Proprietary name under review	28-Aug-2006	Pending
EA	Categorical exclusion granted	N/A	N/A
Microbiology	Acceptable for [redacted]	23-Aug-2006	Bryan Riley
	EES		
[redacted]	Acceptable	03-Feb-2006	Profile
	Acceptable	17-Feb-2006	District File Review
	Acceptable	03-Feb-2006	Profile
	Acceptable	08-Feb-2006	District File Review
	Acceptable	21-Aug-2006	Inspection
Altana Pharma (drug product manufacturing)	Assigned to IB	08-Feb-2006	Pending
[redacted]	Assigned to IB	08-Feb-2006	Pending

The Chemistry Review for NDA 22004

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The application is approvable with an expiration date of 24 months, with revised specifications. Additional information is being requested from the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.
None

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 and is [redacted] It is synthesized from [redacted]

For the nasal spray formulation, the drug substance is [redacted] particle size distribution [redacted]

2. **Drug Product**
The drug product is a hypotonic aqueous suspension, with 120 puff/bottle (commercial) [redacted] presentations and is filled into a [redacted] glass bottle. The drug substance is insoluble in the formulation and is present as fine particles in suspension. The formulation contains microcrystalline cellulose and carboxymethylcellulose sodium NF /(MCC/CMC Na) [redacted] and potassium sorbate/sodium edetate [redacted] The pH is adjusted to [redacted]
The bottle has a plastic outer sleeve to protect against breakage. A plastic pump (with a plastic cap) , which meters the dose, is attached. The whole bottle-pump assembly is packed in an aluminum foil pouch with an oxygen absorber, in order to [redacted] Testing for [redacted] leachables is controlled by extractables testing [redacted] Testing for [redacted] leachables is done on the drug product. See discussion below concerning [redacted] levels.
The pharmaceutical development report (PDR) supports the formulation, the number of priming shots required (in the label), the need for shaking prior to use (in the label) and the drug delivery characteristics: pump delivery (PD), spray content uniformity (SCU), droplet size distribution (DSD), spray pattern (SP) and particle

size distribution (PSD).. The PD ensures that the same volume of drug product is delivered with each spray and the SCU ensures that the same amount of drug is delivered with each spray. The SCU is the basis for the labeled strength of the drug (50 µg). The DSD and the SP ensure that the distribution of the drug in the nasal passages is consistent and reaches the target organ. The PSD does not affect the distribution of the drug in the respiratory system (unlike a metered dose inhaler). The PSD is expected to have minimal impact on the distribution of the drug in the nasal passages and no effect has been demonstrated on drug absorption.
The levels of most impurities are below [redacted] and do not change on storage. The only impurity present on significant amounts is the [redacted] which is a process-related impurity , has been qualified at [redacted] in the review of [redacted] for ciclesonide metered dose inhaler, which is cross-referenced in a letter dated April 20, 2005.
The applicant submitted [redacted] months of stability data on August 10, 2006 for batches manufactured at [redacted] scale to be used as the primary stability data to support the expiration date. They also submitted stability data for batches manufactured at the propose commercial scale of [redacted] on that date. The [redacted] stability data support requested expiration date of 24 months for all parameters except the [redacted]

[redacted]

b. **Description of How the Drug Product is Intended to be Used**
According to the proposed label, the drug product is "indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic in adults and children 2 years of age and older."

[redacted]

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. Additional information is being requested form the applicant to ensure consistency of manufacture and increased assurance of product quality.

III.Administrative Signed off in DFS

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 6

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/s/

Arthur B. Shaw
8/29/2006 12:24:20 PM
CHEMIST
Chem Review #2

Blair Fraser
8/29/2006 02:05:24 PM
CHEMIST

1 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 7

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/s/

Arthur B. Shaw
8/8/2006 01:53:56 PM
CHEMIST
Stability consult for [redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		**REQUEST FOR CONSULTATION**	
TO *(Division/Office)*: OPS New Drug Microbiology Staff		FROM: Arthur Shaw, Review Chemist, ONDQA/DPA1/Branch 2	
DATE August 1, 2006	NDA. 222004	TYPE OF DOCUMENT: Original	DATE OF DOCUMENT December 21, 2005
NAME OF DRUG Ciclesonide nasal spray (no trade name submitted)	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 1	DESIRED COMPLETION DATE August 20, 2006
NAME OF FIRM: Altana Pharma USA			
REASON FOR REQUEST: [redacted] **Effectiveness Evaluation**			

COMMENTS/SPECIAL INSTRUCTIONS:

The applicant has submitted a report in section 3.2.P.2.7.14 (in the EDR) to asses the [redacted] of the formulation target concentrations for [redacted] in the drug product at the pH values of 4.5 and 4.8 when challenged with the USP panel of indicator microorganisms [redacted]

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/s/

Arthur B. Shaw
8/1/2006 02:59:32 PM
CHEMIST

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_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 8

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

/s/

Arthur B. Shaw
7/28/2006 10:36:03 AM
CHEMIST
Tox consult about increased [redacted]

Chemistry Review Cover Sheet

NDA 22-004
[redacted] (ciclesonide) Nasal Spray

Arthur B. Shaw, Ph.D.
ONDQA/DPA1

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-004

2. REVIEW #:1

3. REVIEW DATE: July 25, 2006

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

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Original	21-Dec-2005	Filing Review Complete March 20, 2006
Amendment BC	02-Mar-2006	Response to telephone inquiries regarding [redacted] composition (Feb 10, 2006) and status of manufacturing sites (Feb 21, 2006)
Amendment BC	24-Mar-2006	Partial response to IR letter Mar 17, 2006
Amendment BC	14-Apr-2006	Remainder of response to IR letter
Amendment BC	21-Apr-2006	Partial stability update
Amendment BC	02-Jun-2006	Updated stability, Executed Batch Record, response to IR for [redacted]

FDA Documents	Document Date	Comment
Chemist's Filing Memo	20-Mar-2006	Acceptable for filing. Additional info requested
Addendum to Filing Memo	20-Mar-2006	
IR Letter	17-Mar-2006	Info request from Filing memos

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Pharma, Inc.
Address:	2020 Park Avenue
	Florham Park NJ 07932-0890
Representative:	George Chen
Telephone:	973 514-4240

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NOT PROVIDED
b) Non-Proprietary Name (USAN): ciclesonide
c) Code Names:: BYK20426, B9207-015
d) Chem. Type/Submission Priority
   - Chem. Type: 1
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Nasal spray

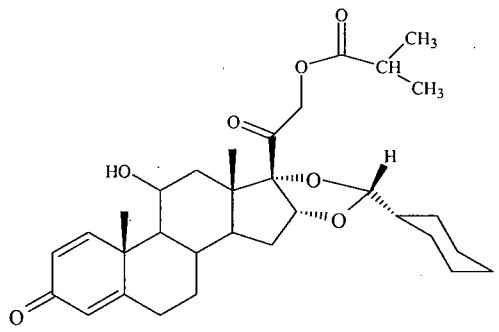
12. STRENGTH/POTENCY: 50 µg

13. ROUTE OF ADMINISTRATION: Intranasal

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



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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Reviewed

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED
	II		Ciclesonide [redacted]	Adequate *	07-Jul-2004
	II		Ciclesonide [redacted] = drug substance	Under review**	
	II			Adequate *	07-Jul-2004
	III			Under review**	
				Under review**	
	III			Under review**	
	III			Under review**	
	III			Under review**	
	III			Under review**	
	III			Under review**	
	III			Under review**	
	III			Under review**	

* IR letter sent Response received. Review pending

** No deficiencies IR letter may be sent

DMFs Not reviewed

DMF #	TYPE	HOLDER	ITEM REFERENCED	Reason for no review
[redacted]	III	[redacted]	[redacted]	[redacted]
	III			
	III			Not in product contact

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	LOA Date
[redacted]			
IND	65,488	Ciclesonide nasal spray	Not necessary held by Altana

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	All sites **ACCEPTABLE** except Altana Pharma [redacted] not inspected yet.	N/A	
Pharm/Tox	Acceptable for leachables	30-Jun-2006	Huiqing Hao
Methods Validation	Not submitted		
DMETS	Proprietary name under review		
EA	N/A		
Microbiology	**N/A**		

The Chemistry Review for NDA 22004

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The application is approvable with an expiration date of [redacted]. Additional information is being requested from the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.
None

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 and is [redacted]. It is synthesized from

[redacted]

For the nasal spray formulation, the drug substance is [redacted] achieve a particle size distribution [redacted]

2. **Drug Product**
The drug product is a hypotonic aqueous suspension, with 120 puff/bottle (commercial) [redacted] presentations and is filled into a [redacted] glass bottle. The drug substance is insoluble in the formulation and is present as fine particles in suspension. The formulation contains microcrystalline cellulose and carboxymethylcellulose sodium NF /(MCC/CMC Na) [redacted] and potassium sorbate/sodium edetate [redacted] The pH is adjusted to optimize the preservative effectiveness of the potassium sorbate.
The bottle has a plastic outer sleeve to protect against breakage. A plastic pump (with a plastic cap) , which meters the dose, is attached. The whole bottle-pump assembly is packed in an aluminum foil pouch with an oxygen absorber, in [redacted]
Testing for [redacted] leachables is controlled by extractables testing of the [redacted]
The pharmaceutical development report (PDR) supports the formulation , the number of priming shots required (in the label), the need for shaking prior to use (in the label) and the drug delivery characteristics: pump delivery (PD), spray content uniformity (SCU), droplet size distribution

(DSD), spray pattern (SP) and particle size distribution (PSD).. The PD ensures that the same volume of drug product is delivered with each spray and the SCU ensures that the same amount of drug is delivered with each spray. The SCU is the basis for the labeled strength of the drug (50 µg). The DSD and the SP ensure that the distribution of the drug in the nasal passages is consistent and reaches the target organ. The PSD does not affect the distribution of the drug in the respiratory system (unlike a metered dose inhaler). The PSD is expected to have minimal impact on the distribution of the drug in the nasal passages and no effect has been demonstrated on drug absorption.

The levels of most impurities are below [redacted] and do not change on storage. The only impurity present on significant amounts is the [redacted] which is a process-related impurity , has been qualified at [redacted] in the review of [redacted] for ciclesonide metered dose inhaler, which is cross-referenced in a letter dated April 20, 2005.

The requested expiration date of 24 months is not supported by the data submitted, since only [redacted] of data have been submitted for review for three batches in each presentation. One batch each has been submitted with 24 months of stability in each presentation.. Based on the data submitted, the drug is stable, showing no trends over time for ciclesonide content, impurities, DSD, or SCU. There are some changes in the sorbate content and the PSD but these are expected to have minimal impact on the overall drug product stability. An expiration date of [redacted] can be granted.

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

According to the proposed label, the drug product is "indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic in adults and children 2 years of age and older." The recommended dose for adults and children [redacted]

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. Additional information is being requested form the applicant to ensure consistency of manufacture and increased assurance of product quality.

III. Administrative Signed off in DFS

182 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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Arthur B. Shaw
7/26/2006 08:30:13 AM
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Blair Fraser
7/26/2006 10:25:22 AM
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/s/

Arthur B. Shaw
4/20/2006 11:09:35 AM
Tox consult for leachables

Division Director Memo
Chemistry, Manufacturing, and Controls

NDA: 22-004

Product: OMNARIS (ciclesonide) Nasal Spray
50 mcg of ciclesonide per emitted dose

Applicant: Altana Pharma, Inc.
2020 Park Avenue
Florham Park NJ 07932-0890

Indication: treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children 2 years of age and older

Presentation: Omnaris contains 50 mcg of ciclesonide per emitted dose.

Each strength is contained in a [redacted] glass bottle fitted with a manual metered pump spray unit. Each bottle contains 120 doses and has a net fill weight of [redacted] grams. Each complete assembly is individually packaged in an aluminum foil pouch containing an oxygen absorber.

[redacted]

EER Status: Pending

Original Submission: 21-DEC-2005

Ciclesonide, a corticosteroid, has the chemical name (2'R)-2'-Cyclohexyl-11ß-hydroxy-21-isobutyryloxy-16βH-dioxolo[5',4':16,17]pregna-1,4-diene-3,20-dione. Ciclesonide is a white to yellow-white powder with a molecular weight of 540.69 Daltons, an empirical formula $C_{32}H_{44}O_7$ and exists as a single, [redacted]

[redacted]

[redacted] The drug substance [redacted] achieve a particle size distribution [redacted]

Conclusion: Drug substance is acceptable

Omnaris Nasal Spray is a metered-dose, manual-pump spray assembly containing [redacted], hypotonic aqueous suspension of ciclesonide that delivers 50 mcg per actuation. The drug product is supplied as 120 puff/bottle (commercial) and

[redacted] presentations and is filled into [redacted] glass bottle. The drug substance is present as fine particles suspended in a aqueous solution containing microcrystalline cellulose NF, carboxymethylcellulose sodium NF, and hypromellose USP [redacted] The pH is adjusted [redacted] Specifications are considered acceptable.

Labeling for the package insert, container labels, and carton labels is acceptable.

Expiry of 24 months for drug product (complete container) and 4 months for the drug product out of container is supported by submitted stability data; statistical analysis by Biometrics staff confirms this expiry. An agreement was made to provide additional stability data as they become available.

All associated Drug Master Files (DMFs) are acceptable.

Conclusion: Drug product is acceptable

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval,** pending a satisfactory cGMP status.

Chi-wan Chen, Ph.D.
Acting Division Director
DPA I/ONDQA

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/s/

Blair Fraser
10/16/2006 11:22:34 AM
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Chi Wan Chen
10/16/2006 02:43:46 PM
CHEMIST