CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-124s000

CHEMISTRY REVIEW(S)

Chemistry Review Cover Sheet

NDA 22-124
Omnaris (ciclesonide) Nasal Spray

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

Chemistry Review Data Sheet

1. NDA 22-124

2. REVIEW #2

3. REVIEW DATE: November 16, 2007

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

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Applicant's Submission Number	Document Date	Comment
Amendment AZ	0002	24-May-2007	Response to Clinical Deficiencies in original NDA

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Pharma, Inc.
Address:	2020 Park Avenue Florham Park NJ 07932-0890
Representative:	Cheryl Czachorowski.
Telephone:	973 514-4271

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: 6
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Nasal spray

12. STRENGTH/POTENCY: 50 μg

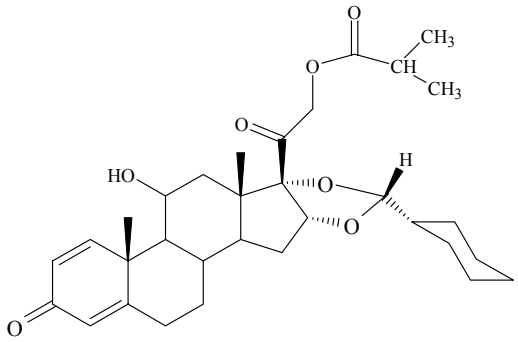
13. ROUTE OF ADMINISTRATION: Intranasal

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: All the DMFs were reviewed in support of NDA 22004, the original NDA for this product, were found acceptable and have had no significant changes since then.

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	II		(b) (4)
	II		
	II		
	III		
	III		
	III		
	III		
	III		
	III		
	III		
	III		

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	LOA Date
IND	53,391	Ciclesonide MDI	20-Apr-2005
NDA	21658		

(b) (4)

18. STATUS:

All Consults and CMC Related Reviews were done for NDA 22004. There have been changes.

All manufacturing sites were found Acceptable for NDA 22004 on November 14, 2007.

The Chemistry Review for NDA 22124

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.. All inspections have been completed and all sites are **ACCEPTABLE**

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

None

II. Summary of Chemistry Assessments

Note: This information is the same as for NDA 22004 for the same drug product.

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 photolabile. It is synthesized from α-hydroxyprednisolone by a) esterification of the 21 hydroxyl with isobutyric acid and b) formation of a stereospecific double ketal with cyclohexane on the 16,17 hydroxyls, yielding the R-epimer.

For the nasal spray formulation, the drug substance is (b) (4) to achieve a particle size distribution (b) (4).

2. Drug Product

The drug product is a hypotonic aqueous suspension, with 120 puff/bottle (commercial) (b) (4) presentations and is filled into a brown 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) (b) (4) and potassium sorbate/sodium edetate (b) (4)

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 prevent oxidation of the potassium sorbate. Testing for pump additive leachables is controlled by extractables testing of the pump components. Testing for (b) (4) (leachable) (b) (4) (impurity) is done on the drug product. See discussion below concerning (b) (4) 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 (b) (4) and do not change on storage. The only impurity present on significant amounts is the (b) (4) ciclesonide, which is a process-related impurity. It has been qualified at (b) (4) in the review of NDA 21-658 for ciclesonide metered dose inhaler, which is cross-referenced in a letter dated April 20, 2005.

The applicant submitted 18 months of stability data on August 10, 2006 for batches manufactured at (b) (4) 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 (b) (4). The (b) (4) stability data support requested expiration date of 24 months for all parameters except the (b) (4) level. On July 21, 2006 the applicant submitted a "Failure Investigation Report" as a result of levels of (b) (4) being out of specification for one of the (b) (4) batches at 3 months. Subsequent investigation found that the (b) (4) formation was increased when the drug product was stored out-of-pouch (OOP) i.e. during patient use. The (b) (4) had not been tested for in the studies (in the PDR) that qualified the 6 month out-of pouch storage period. Those studies had only been done to assess the effect of OOP storage on potassium sorbate in terms of its (b) (4) effectiveness. The applicant has requested acceptance criteria of (b) (4) for up to 24 months storage in-pouch and (b) (4) for 6 months out-of-pouch storage. The toxicological evaluation of these levels found them to be acceptable . However, there is not enough stability data to support these proposed levels. In view of the limited stability data available, an expiration date of 24 months (with a (b) (4) acceptance criterion) and an out-of-pouch storage time (with a (b) (4) acceptance criterion) of four

months was recommended to the applicant. These recommendations were accepted by the applicant. Additional stability data will be needed to support an increase in the (b) (4) level on long-term in-pouch storage and extension of the out-of-pouch storage time.

All sites for manufacturing and testing were found were found acceptable on November 14, 2007. (attached)

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

This application adds a new use: "Treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older**."** The previously indication for "treatment of nasal symptoms associated with perennial allergic rhinitis in adults and children 12 years of age and older" (emphasis added) remains unchanged. The recommended dose for all patients is 200 µg/day. (b) (4)

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

6 Page(s) have been Withheld in Full following this page as B4 (TS)

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
11/16/2007 02:17:08 PM
CHEMIST
Review #2 EER Acceptable

Ali Al-Hakim
11/16/2007 06:08:54 PM
CHEMIST

Chemistry Review Cover Sheet

NDA 22-124
Omnaris (ciclesonide) Nasal Spray

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

Chemistry Review Data Sheet

1. NDA 22-124

2. REVIEW #1

3. REVIEW DATE: November 9, 2007

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

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Applicant's Submission Number	Document Date	Comment
Amendment AZ	0002	24-May-2007	Response to Clinical Deficiencies in original NDA

7. NAME & ADDRESS OF APPLICANT:

Name:	Altana Pharma, Inc.
Address:	2020 Park Avenue Florham Park NJ 07932-0890
Representative:	Cheryl Czachorowski.
Telephone:	973 514-4271

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: 6
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Nasal spray

12. STRENGTH/POTENCY: 50 μg

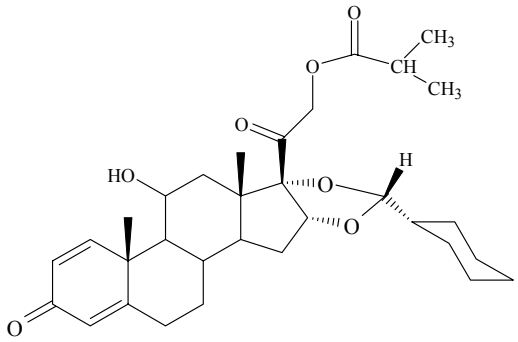
13. ROUTE OF ADMINISTRATION: Intranasal

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: All the DMFs were reviewed in support of NDA 22004, the original NDA for this product, were found acceptable and have had not significant changes since then.

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	II		(b) (4)
	II		
	II		
	III		
	III		
	III		
	III		
	III		
	III		
	III		
	III		

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	LOA Date
IND	53,391	Ciclesonide MDI	20-Apr-2005
NDA	21658		

(b) (4)

18. STATUS:

All Consults and CMC Related Reviews were done for NDA 22004. There have been changes.

All manufacturing sites were found Acceptable for NDA 22004. Update requests have been sent. Two sites are still "Pending" in EES. The others are Acceptable.

(b) (4)

The Chemistry Review for NDA 22124

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

Note: This information is the same as for NDA 22004 for the same drug product.

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 photolabile. It is synthesized from α-hydroxyprednisolone by a) esterification of the 21 hydroxyl with isobutyric acid and b) formation of a stereospecific double ketal with cyclohexane on the 16,17 hydroxyls, yielding the R-epimer.

For the nasal spray formulation, the drug substance is (b) (4) to achieve a particle size distribution (b) (4).

2. Drug Product

The drug product is a hypotonic aqueous suspension, with 120 puff/bottle (commercial) (b) (4) presentations and is filled into a brown 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) (b) (4) and potassium sorbate/sodium edetate (b) (4)

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 prevent oxidation of the potassium sorbate. Testing for pump additive leachables is controlled by extractables testing of the pump components. Testing for (b) (4) (leachable) (b) (4) (impurity) is done on the drug product. See discussion below concerning (b) (4) 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 (b) (4) and do not change on storage. The only impurity present on significant amounts is the (b) (4) ciclesonide, which is a process-related impurity. It has been qualified at (b) (4) in the review of NDA 21-658 for ciclesonide metered dose inhaler, which is cross-referenced in a letter dated April 20, 2005.

The applicant submitted 18 months of stability data on August 10, 2006 for batches manufactured at (b) (4) 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 (b) (4). The (b) (4) stability data support requested expiration date of 24 months for all parameters except the (b) (4) level. On July 21, 2006 the applicant submitted a "Failure Investigation Report" as a result of levels of (b) (4) being out of specification for one of the (b) (4) batches at 3 months. Subsequent investigation found that the (b) (4) formation was increased when the drug product was stored out-of-pouch (OOP) i.e. during patient use. The (b) (4) had not been tested for in the studies (in the PDR) that qualified the 6 month out-of pouch storage period. Those studies had only been done to assess the effect of OOP storage on potassium sorbate in terms of its (b) (4) effectiveness. The applicant has requested acceptance criteria of (b) (4) for up to 24 months storage in-pouch and (b) (4) for 6 months out-of-pouch storage. The toxicological evaluation of these levels found them to be acceptable . However, there is not enough stability data to support these proposed levels. In view of the limited stability data available, an expiration date of 24 months (with a (b) (4) acceptance criterion) and an out-of-pouch storage time (with a (b) (4) acceptance criterion) of four

months was recommended to the applicant. These recommendations were accepted by the applicant. Additional stability data will be needed to support an increase in the (b) (4) level on long-term in-pouch storage and extension of the out-of-pouch storage time.

All sites for manufacturing and testing were found were found acceptable for NDA 22004 in October 2006. An EER was submitted to the Office of Compliance for all the sites. Requests for GMP inspections for the sites for (b) (4) of the drug substance (b) (4) and for sterility testing of the finished dosage form (b) (4) were submitted to the District Office by the Office of Compliance.

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

This application adds a new use: "Treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older**."** The previously indication for "treatment of nasal symptoms associated with perennial allergic rhinitis in adults and children 12 years of age and older" (emphasis added) remains unchanged. The recommended dose for all patients is 200 µg/day. (b) (4)

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

1 Page has been Withheld in Full following this page as B4 (TS)

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
11/9/2007 02:14:14 PM
CHEMIST
Chem Review #1

Ali Al-Hakim
11/9/2007 02:35:25 PM
CHEMIST