CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-124s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-124 SUPPL # HFD # 570

Trade Name OMNARIS

Generic Name ciclesonide

Applicant Name Nycomed

Approval Date, If Known 11/ /2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 22-004 OMNARIS

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

M1-403
M1-417
M1-405
M1-416

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

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

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

Investigation #1 YES ☒ NO ☐

Investigation #2 YES ☐ NO ☒

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

M1-403 and M1-405 under NDA 22-004

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

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

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

Investigation #1		!
		!
IND # 65488	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

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

Investigation #1	!
	!

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Colette Jackson
Title: Regulatory Health Project Manager
Date: 11/14/2007

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director, DPAP

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

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

/s/

Badrul Chowdhury

11/21/2007 03:38:38 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # 22-124 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: May 24, 2007 Action Date: November 24, 2007

HFD 570 Trade and generic names/dosage form: OMNARIS (ciclesonide) Nasal Spray

Applicant: Nycomed Therapeutic Class: 6S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Seasonal Allergic Rhinitis

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **✓ No: Please check all that apply: ✓Partial Waiver ___Deferred ✓ Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo. 0 yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr. <2 Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **✓ Disease/condition does not exist or is difficult to diagnose in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr.__>2__ Tanner Stage_____
Max_Adult kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Perennial Allergic Rhinitis

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **✓ No: Please check all that apply: ✓Partial Waiver ____Deferred ✓Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo. 0**	**yr.**	**Tanner Stage**
Max	**kg**	**mo.**	**yr. <2**	**Tanner Stage**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **✓ Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr.__>2__ Tanner Stage_____
Max_Adult_ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

I

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 22-124
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-796-1654.

(revised 10-14-03)

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

/s/

Colette Jackson

11/23/2007 11:27:58 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2007

To: Cheryl Czachorowski Senior Manager, Regulatory Affairs	**From:** Colette Jackson
Company: ALTANA PHARMA	Division of Pulmonary and Allergy Products
Fax number: 973-236-1695	**Fax number:** 301-796-9718
Phone number: 973-514-4271	**Phone number:** 301-796-1230

Subject: NDA 22-124 FDA Proposed Package Insert

Total no. of pages including cover: 17

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-124
Ciclesonide Nasal Spray

Please refer to your May 24, 2007, new drug application (NDA) for ciclesonide nasal spray. We acknowledge your submission dated November 9, 2007. Please refer to the enclosed labeling with our preliminary labeling comments and/or recommendations. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling.

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

Enclosure: Recommendations to the Proposed Label

15 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

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

/s/

Ladan Jafari
11/19/2007 03:02:05 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 22-124	Efficacy Supplement Type SE-	Supplement Number	
Drug: OMNARIS (ciclesonide) Nasal Spray		Applicant: Nycomed US Inc.	
RPM: Colette Jackson		HFD-570	Phone # 6-1230

Application Type: **(x)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(x)** Standard **( )** Priority
• Chem class (NDAs only)	6
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	11/24/2007
❖ Special programs (indicate all that apply)	**(x)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(x)** Paid UF ID number _3006285__
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) _____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(x)** No

• This application is on the AIP	**( )** Yes **(x)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(x)** Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(x)** Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **( )** Verified 21 CFR 314.50(i)(1) **( )** (ii) **( )** (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	**( )** N/A (no paragraph IV certification) **( )** Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	**( )** Yes **( )** No **( )** Yes **( )** No **( )** Yes **( )** No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	**( )** Yes **( )** No **( )** Yes **( )** No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	**( )** Yes, Application #_____ **(x)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	**(x)** AP **( )** TA **( )** AE **( )** NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	**(x)** Materials requested in AP letter **( )** Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(x)** Yes **( )** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None **( )** Press Release **( )** Talk Paper **( )** Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	10/25/2007
• Most recent applicant-proposed labeling	11/ 20/2007
• Original applicant-proposed labeling	5/24/2007
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	11/19 /2007 (DMETS) 6/29/2007(DDMAC)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	7/3/2007, 7/13/2007, 10/17/2007, 10/30/2007 and 11/19 /2007
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	10/1/03
• Pre-NDA meeting (indicate date)	8/29/2005 (CMC), 6/7/2005
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	CMC-9/29/2006 P/T- 9/8/2006 and 10/30/2007 MO- 9/22/2006 STATS- 11/6/2007 CDTL- 11/21 /2007 DD- 11/21 /2007 ODD-10/20/2006
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	2/23/2006, 9/5/2006, 7/9/2007, and 10/12/2007
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	2/24/2006
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	3/1/2006, 8/29/2006, and 11/6/2007
❖ Biopharmaceutical review(s) *(indicate date for each review)*	8/28/2006, 9/8/2006, and 11/7/2007
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	8/15/2006 and 11/1/2007
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	3/20/2006 (2), 7/26/2006, 8/29/2006, 9/29/2006, 10/16/2006, and 11/9/2007
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	8/23/2006
❖ Facilities inspection (provide EER report)	Date completed: 10/20/2006 **(x)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **(x)** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	2/14/2006, 9/1/2006, and 10/29/2007
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 10/31/07

TO: Colette Jackson, Regulatory Project Manager
Carol Bosken, M.D., Clinical Reviewer
Division of Pulmonary and Allergy Drug Products, HFD-570

THROUGH: Joseph Salewski
Deputy Director
Division of Scientific Investigations/HFD-45

FROM: Tejashri Purohit-Sheth, M.D.
Medical Officer
Good Clinical Branch 2/HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 22-124

NME: No

APPLICANT: Altana, Inc.

DRUG: OMNARIS™ (ciclesonide nasal spray)

THERAPEUTIC CLASSIFICATION: Priority

I**NDICATION**: Treatment of symptoms associated with allergic rhinitis in patients (b) (4) years of age and older

CONSULTATION REQUEST DATE: 07/12/07

DIVISION ACTION GOAL DATE: 11/19/07 (revised)

PDUFA DATE: 11/23/07

I. BACKGROUND:

Altana Inc. submitted this New Drug Application for the use of Ciclesonide Nasal Spray (OMNARIS™) in the treatment of nasal symptoms associated with allergic rhinitis in patients 6 to 11 years of age. An application for Ciclesonide Nasal Spray for the treatment of symptoms of allergic rhinitis in patients (b years of age and older, was submitted in December 2005 and was approved in October 2006 in patients 12 years of age and older. However, due to lack of demonstrated efficacy in children younger than 12 years of age, the indication for this age group was not approved. This application includes data to support the pediatric indication in patients 6 to 11 years of age.

The pivotal study in support of the proposed indication in the pediatric population 6 to 11 years of age is M1-417. The pivotal study was audited due to concerns regarding the reliability of the data collected in support of efficacy. The concern stemmed from the manner in which the data was collected. The primary efficacy variable was the 12-hour mean AM and PM reflective TNSS as recorded by the parent/caregiver. The symptom scores were recorded with an automated telephone interactive voice response system (IVRS). The application states that Perceptive Informatics designed the IVRS and was responsible for data collection and forwarding the data to the sponsor. The use of this IVRS was concerning for the following reasons:

1. This automatic telephone recorded data collection has never been used in this drug's development program and no validation data for the use of this system have been submitted in support of this application.
2. The printed description of the symptoms provided to the caregivers is inconsistent with those received from the automated telephone system. The individual nasal symptoms should have been scored on a 0 to 3 scale described as none, mild, moderate, and severe. However, the scale used by the IVRS was scored: none, very mild, moderate, and severe. These discrepancies were noted in the printed instructions given to the parents/caregivers provided in the NDA.

The three investigator sites–3872 (Dr. Jeffrey Wald), 4777 (Dr. William Storms), and 3482 (Dr. Ita Tripathy) were selected for audit based on the relatively large number of subjects enrolled at these sites and discrepancies noted in the amount of missing symptom diary data relevant to investigator comments.

II. RESULTS (by protocol/site)**:**

Name of CI /Sponsor/CRO and site #, if known	**City, State***	**Protocol #**	**Insp. Date**	**EIR Received Date**	**Final Classification**
Jeffrey Wald, M.D./#3872	Overland, KS	M1-417	7/30/07-8/03/07	8/24/07	NAI
Ita Tripathy, M.D./#3482	Rolla, MO	" "	8/28/07-8/30/07	9/24/07	NAI
William Storms, M.D./#4777	Colorado Springs, CO	" "	Unknown	Pending	Pending
Perceptive Informatics, Inc.	Lowell, MA	" "	Unknown	Pending	Pending

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. **Protocol M1-417**: *A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Clinical Trial Designed to Assess the Safety and Efficacy of Ciclesonide (200 mcg and 100 mcg, once daily) Applied as a Nasal Spray for Two Weeks in the Treatment of Seasonal Allergic Rhinitis (SAR) in Patients 6 to 11 Years of Age*

1. **JEFFREY WALD, M.D.** [Site # 3872; # of subjects: 16]
   8675 College Boulevard/Suite 200
   OverlandPark, KS 66210

a. What was inspected

A total of 16 subjects were randomized at this site, of which 15 completed the study. One subject discontinued due to an adverse event (worsening asthma symptoms). All study subject records were reviewed. The following were evaluated for all subjects: drug accountability records, IRB approval paperwork, eligibility criteria, adverse event reporting, efficacy data in comparison to data listings provided in the NDA, randomization and blinding procedures, and clinical investigator oversight.

b. Limitations of inspection

None

c. General observations/commentary

In general, the clinical investigator complied with applicable regulations. There were no significant discrepancies documented. The investigation documented that: the clinical investigator had adequate oversight and took an active role in the study; that subjects were appropriately randomized; blinding procedures were followed; subjects met eligibility criteria; diagnosis of SAR was confirmed in all subjects; adverse events were appropriately reported; IRB approval was appropriately obtained and maintained; and drug was appropriately dispensed/collected. Additionally, the inspection verified that the efficacy endpoints as reported in the NDA were consistent with source documents.

Note that for all subjects there was a discrepancy between source documentation and the Date of Last Dose reported in Data Listing 16.2.5.1. The investigator captured the date correctly on the CRF. It appears that the IVRS did not capture the date of the last dose the following morning, resulting in incorrect dates documented in Data Listing 16.2.5.1. For example, Subject #6682 has a last dose in source documents as 26 June 2006; however, Data Listing 16.2.5.1 lists the date of last dose as 25 June 2006. For the majority of subjects, the date of last dose is discrepant by only one day. For Subjects 7942 and 7944, the dates are discrepant by 2 days.

There were no other significant findings at this site. No Form FDA 483 was issued.

d. Assessment of data integrity:

The data from this site are considered reliable in support of this application. It is unlikely that the discrepancy with respect to date of last dose will affect data integrity; however, the determination of the clinical relevance of this finding is deferred to the review division.

2. SANCHAYITA TRIPATHY, M.D. [Site # 3482; # of subjects: 18]
8675 College Boulevard/Suite 200
OverlandPark, KS 66210

a. What was inspected

A total of 18 subjects were randomized at this site, of which 18 completed the study. There were no reported AEs at this site. All study subject records were reviewed. The following were evaluated for all subjects: drug accountability records, IRB approval paperwork, eligibility criteria, adverse event reporting, efficacy data in comparison to data listings provided in the NDA, randomization and blinding procedures, and clinical investigator oversight.

b. Limitations of inspection

None

c. General observations/commentary

In general, the clinical investigator complied with applicable regulations. There were no significant discrepancies documented. The investigation documented: that the clinical investigator had adequate oversight and took an active role in the study; that subjects were appropriately randomized; blinding procedures were followed; subjects met eligibility criteria; diagnosis of SAR was confirmed in all subjects; adverse events were appropriately reported; IRB approval was appropriately obtained and maintained; and drug was appropriately dispensed/collected. Additionally, the inspection verified that the efficacy endpoints as reported in the NDA were consistent with source documents.

Note that for all, except one (#7757), there was a discrepancy between source documentation and the Date of Last Dose reported in Data Listing 16.2.5.1. The investigator captured the date correctly on the CRF. It appears that the IVRS did not capture the date of the last dose the following morning, resulting in incorrect dates documented in Data Listing 16.2.5.1. For example, Subject #7758 has a last dose in source documents as 05 May 2006; however, Data Listing 16.2.5.1 lists the date of last dose as 04 May 2006. For all of the subjects, the date of the last dose is discrepant by only one day.

There were no other significant findings at this site. No Form FDA 483 was issued.

d. Assessment of data integrity:
The data from this site are considered reliable in support of this application. It is unlikely that the discrepancy with respect to date of last dose will affect data integrity; however, the determination of the clinical relevance of this finding is deferred to the review division.

3. WILLIAM STORMS, M.D.
1625 Medical Center Point/Suite 190
Colorado Springs, CO 80907

a. What was inspected
A total of 13 subjects were screened at this site, of which 7 were randomized.

b. Limitations of inspection
The EIR was not available at the time this CIS was written. The findings are based on preliminary communications with the FDA field investigator.

c. General observations/commentary
In general, the clinical investigator complied with applicable regulations. There were no significant discrepancies documented. No Form FDA 483 was issued to the investigator.

There were no other significant findings at this site per preliminary email from the field inspector.

d. Assessment of data integrity:
The data from this site are considered reliable in support of this application.

4. (b) (4)

a. What was inspected
During this inspection, the following were reviewed: 1) the contract between the CRO and sponsor to verify that the CRO met its obligations; 2) project specific and validation plans; 3) testing strategy and test plans; 4) test scripts validation summary reports for both the core and project IVRS applications; 5) change control requests; 6) data transfer; and 7) SOPs related to quality and IVRS development.

Additionally, a data audit of data reported in 16.2.6.2 Listing of Patient Diary was done for the three sites identified on the consult from the review division. Of the 18 subjects randomized at Site 3482, a comparison of source documentation to the data listing was done for 11 subjects. Of the 16 subjects randomized at Site 3872, a comparison between the data listing and source documents was done for 9 subjects. Of the 18 subjects randomized at Site 4777, a comparison between the data listing and source documents was done for 9 subjects.

b. Limitations of inspection
The EIR was not available at the time this CIS was written. The findings are based on preliminary communications with the FDA field investigator.

c. General observations/commentary
In general, the CRO complied with applicable regulations. There were no significant discrepancies documented.

The following are general findings from the inspection as conveyed via preliminary communication by the field investigator:

- The IVRS is a fully validated system based on evaluation of the Validation Summary reports for the core application, Project Validation Plan, Testing/Strategy/Plan, Test Scripts, Testing Data, and Testing Summary Reports.

- The system is a closed system with an audit trail. It is a secure system with uninterruptible power supply and replicates itself every 10 minutes with incremental back up every day and full back up every other week. The firm has a disaster recovery plan. There is anti-virus software on the system and there have been no major viruses on the server in the past four years.

- Training was provided by the CRO to the clinical investigators/staff at the Investigators' Meeting. Caretakers were provided with a "Welcome Package" at the Screening visit, which included the "Diary User Quick Reference Guide" that described how to use the IVRS.

- Data audits for Patient Diary listings 16.2.6.2 for Sites 3482, 3872 and 4777, did not reveal any discrepancies. Source documentation confirmed the data provided in the NDA.

- Alert fax memos were supposed to be sent to the site when subjects had missed two calls. However, this was not always sent after two missed calls. Specifically, if the first missed call was from the morning, sites did not receive the alert fax until after the third missed call. The firm investigated this matter and provided an explanation of what occurred and was able to show that it occurred infrequently. It appeared to not have a major impact on investigator notification.

- The IVRS was available from 0500-1300 and 1700-0100. Subjects were told to call between 0500-1200 and 1700-0001. The extra hour window was created to allow subjects access to the IVRS if they forgot to call or needed to have problem resolved.

The following are specific questions addressed by the field investigator in response to CDER's (DSI and Review Division) requests for evaluation:

- The printed description of the symptoms provided to the caregivers was inconsistent with those received from the IVRS.

    - According to the contract with the sponsor, the diary questions were formalized and approved by the sponsor during the IVRS development. In an email from the sponsor to the CRO, the sponsor took responsibility for the inconsistency between the printed and audio version of the description of symptoms. The sponsor had final review and approval of the printed document and requirement specifications of the IVRS.

- Some caregivers complained that they were unable to call into the IVRS.

    - The CRO has a call center which caretakers were able to contact in the event that they had any problems with the IVRS. Documentation of the calls included summary of the problem, time of occurrence and resolution and the solution to the problem.

    - The field investigator specifically looked at Subject 7942 (Site 3872) call records to the IVRS, since this subject's mother had reported to the site that she had problems getting into the IVRS on 4/25/06. Per review of the records at **(b) (4)**, there were no calls from this caretaker or the site recorded in the "Remedy Call Center Tracking" system. According to source documentation, calls were made for this subject on 4/20-22 (AM and PM), 4/23 (PM), 4/24 (AM), 4/25-5/5 (AM and PM), 5/7 (AM), 5/8 (PM), 5/9-5/10 (AM and PM), and 5/11-5/12 (AM). If she had difficulty calling into the IVRS, she apparently did not call the IT help ("Remedy Call Center Tracking" system).

- The FDA investigator was requested to evaluate why the date of the last dose as documented by the source documents at Sites 3872 and 3482, did not match the "Date of Last Dose" in Data Listing 16.2.5.1 (Listing of Study Medication).

    - The date recorded in 16.2.5.1 is the last dose that was recorded in the IVRS. The last dose taken by the subject as documented in source documentation at the study sites, was not recorded in the IVRS system. The subject took the last dose in the morning of the last visit. At the conclusion of the visit, the subject was then discontinued from the IVRS system by the site. Therefore there was no evening call by the caretaker to the IVRS (which is when the time of the morning dose was recorded for all of the other days prior to the last visit).

- In Listing 16.2.4.8, several investigators noted that the caregiver claimed to have administered the medication correctly; however, it was not recorded correctly in the IVRS.

    - The field investigator reviewed the records of all 13 subjects that reportedly had this issue. She found that in most cases, there were no calls in the evening made to the IVRS, the point in time when the time of the morning dose was recorded. It appears that the CI reviewed the "Subject Review Report" (the document generated by the IVRS documenting drug doses and symptom scores) and asked the caretaker if the subject had received the dose and the caretaker claimed that the subject had taken the dose, when in fact they had forgotten to call the IVRS to report the dose.

- Site 5205 had medication times reported at 2415 and 2435 for some subjects.

    - Source documentation at the CRO shows that the times were reported at the 24th hour in the IVRS. It appears that the data management CRO **(b) (4)** added 12 to all of the doses reported as taken in the PM resulting in all doses taken between 12:00 and 12:59 am (midnight) reported as 24:00-24:59.

There were no other significant findings at this site per preliminary email from the field inspector. No Form FDA 483 was issued to the investigator.

d. Assessment of data integrity

Per evaluation of the IVRS, it appears that it is a fully validated system, and the data as recorded by the IVRS is considered reliable in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. No significant discrepancies were documented. Additionally, the IVRS was reported to be a fully validated system and no significant issues were identified with respect to this system. Some minor issues as identified above, are unlikely to affect data integrity; however, the clinical impact will need to be evaluated by the review division.

Follow-Up Actions:

Observations noted above for Dr. Storms' site and **(b) (4)** are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Medical Officer
GCP 2/HFD-47
Division of Scientific Divisions

CONCURRENCE:

{See appended electronic signature page}

Joseph Salewski
Deputy Director
Division of Scientific Investigations/HFD-45

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/s/

Tejashri Purohit-Sheth
11/1/2007 01:16:53 PM
MEDICAL OFFICER

Joseph Salewski
11/1/2007 04:05:17 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 30, 2007

To: Cheryl Czachorowski Senior Manager, Regulatory Affairs	**From:** Colette Jackson
Company: ALTANA PHARMA	Division of Pulmonary and Allergy Products
Fax number: 973-236-1695	**Fax number:** 301-796-9718
Phone number: 973-514-4271	**Phone number:** 301-796-1230

Subject: NDA 22-124 Pharmacology/Toxicology Comment

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-124
Ciclesonide Nasal Spray

Please refer to your May 24, 2007, new drug application (NDA) for ciclesonide nasal spray. We also refer to your October 22, 2007, submission which requests clarification regarding revisions to the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the proposed product label. We have the following comment.

The calculation for the exposure ratios of rat and human doses using body surface area comparisons is based on the following formula:

$$\frac{\text{Rat dose (mg/kg) x rat factor (kg/m}^2\text{)}}{\text{Human dose (mg/kg) x human factor (kg/m}^2\text{)}}$$

The term "factor" in the formula refers to body surface area conversion factor which is 6 kg/m^2 for rats, 37 kg/m^2 for humans age 12 years and older and 25 kg/m^2 for humans 6 to 11 years of age.

Human body weight is assumed to be 50 kg for ages 12 years and older and 20 kg for 6 to 11 year old subjects;

For example, for a 6 year old patient, the exposure ratio for the current NDA is:

$$\frac{0.193 \text{ mg/kg x 6 kg/m}^2}{0.2 \text{ mg/20kg x25 kg/m}^2}$$

The result of 4.6 is rounded to 5.

The following table presents the exposure ratios of carcinogenicity studies.

Drug: **OMNARIS**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	6	0.2	1	0.2	20	0.01	25	0.25
Adult	>12	0.2	1	0.2	50	0.004	37	0.148

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	IH	0.193	6	1.158	7.8243	4.632		
mouse	po	0.9	3	2.7	18.243	10.8		

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	50	37	rabbit	12		
Adult	50	37	rat	6		

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

Drafted: CCJ/ October 23, 2007
Initialed:
Barnes/ October 24, 2007
Hao/ October 25, 2007
McGovern/ October 25, 2007

Finalized: CCJ/ October 30, 2007
Filename: 22124 October 2007 PT fax

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/s/

Colette Jackson
10/30/2007 02:26:31 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 25, 2007

To: Cheryl Czachorowski Senior Manager, Regulatory Affairs	**From:** Colette Jackson
Company: ALTANA PHARMA	Division of Pulmonary and Allergy Products
Fax number: 973-236-1695	**Fax number:** 301-796-9718
Phone number: 973-514-4271	**Phone number:** 301-796-1230

Subject: NDA 22-124 FDA Proposed Package Insert

Total no. of pages including cover: 15

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-124
Ciclesonide Nasal Spray

Please refer to your May 24, 2007, new drug application (NDA) for ciclesonide nasal spray. We acknowledge your submission dated October 23, 2007. Please refer to the enclosed labeling with our preliminary labeling comments and/or recommendations. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling. The following comments provide our rationale for the labeling changes.

1. All of the secondary efficacy outcome measures were deleted from Table 3 to improve the clarity of presentation. The secondary outcome measures were not consistent and they are difficult to interpret without a detailed description of the study results. The instantaneous TNSS was included in Table 2 to show effectiveness of OMNARIS throughout the dosing interval. This need not be repeated in the pediatric results section.

2. The PAR results were deleted from Table 3 because the purpose of this tabular information is to assist physicians in prescribing. OMNARIS is not being approved for the treatment of PAR in patients less than 12 years of age, therefore, the information should not be included in this table.

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

Enclosure: Recommendations to the Proposed Label

15 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

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/s/

Colette Jackson
10/25/2007 12:43:10 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-124

ALTANA Pharma
210 Park Avenue
Florham Park, NJ 07932

Attention: Cheryl Czachorowski
Senior Manager, Regulatory Affairs

Dear Ms. Czachorowski:

Please refer to your new drug application (NDA) dated December 21, 2005, received December 22, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OMNARIS (ciclesonide) Nasal Spray.

We acknowledge receipt of your submissions dated March 2, 17, 21, 24, and 30, April 7, 14, and 21, May 4, June 2, 6, and 21 (2), July 21 and 25, August 2, 4, 10, 11, 14, 17, 18, 21, 22, and 29, September 13, 15, 18, 22, 26, and 29, and October 6, 10, 13, 17, and 19 (3), 2006.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, the following deficiency must be satisfactorily addressed.

The submitted clinical studies do not support efficacy and safety of ciclesonide nasal spray for ages (b) (4) through 11 years. The clinical studies in patients (b) (4) through 11 years of age failed to show convincing evidence of efficacy at any of the doses tested. (b) (4)

(b) (4)

In addition, it will be necessary for you to submit revised draft labeling incorporating the information from the studies requested above.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to

the Division of Pulmonary and Allergy Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs

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/s/

Curtis Rosebraugh

10/20/2006 06:46:26 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 17, 2007

To: Cheryl Czachorowski Senior Manager, Regulatory Affairs	**From:** Colette Jackson
Company: ALTANA PHARMA	Division of Pulmonary and Allergy Products
Fax number: 973-236-1695	**Fax number:** 301-796-9718
Phone number: 973-514-4271	**Phone number:** 301-796-1230

Subject: NDA 22-124 FDA Proposed Package Insert

Total no. of pages including cover: 18

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-124
Ciclesonide Nasal Spray

Please refer to your May 24, 2007, new drug application (NDA) for ciclesonide nasal spray. Please refer to the enclosed labeling with our preliminary labeling comments and/or recommendations. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling.

(b) (4)

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

Enclosure: Recommendations to the Proposed Label

15 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

Drafted: CCJ/October 16, 2007
Initialed:

Barnes/ October 16, 2007
Bosken/ October 16, 2007
Gilbert-McClain/ October 16, 2007
Roy/ October 17, 2007
Qiu/ October 17, 2007
Zhou/ October 17, 2007
Li/ October 17, 2007
Hao/ October 16, 2007
McGovern/ October 17, 2007
Shaw/ October 16, 2007
Peri/ October 16, 2007
Chowdhury/ October 16, 2007

Finalized: CCJ/ October 17, 2007

Filename: 22124 October 2007 labeling fax.doc

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/s/

Colette Jackson
10/17/2007 12:02:50 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS

FROM: Colette Jackson
Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 17, 2007		22-124	N	May 24, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
OMNARIS (ciclesonide)	Standard	Pro-corticosteroid	October 5, 2007

NAME OF FIRM: Altana Pharma

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Labeling Review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
This is a request for an evaluation and review of the labeling for OMNARIS (ciclesonide).
The labeling is being updated to include information for patients 6 to 11 years of age.
This submission is electronic only and is located in the EDR in the submission dated May 24, 2007.

PDUFA DATE: November 23, 2007

CC:
Archival NDA 22-124
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Colette Jackson
9/17/2007 10:37:34 AM

DSI CONSULT: Request for Clinical Inspections

Date: July 12, 2007

To: Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: Colette Jackson, Regulatory Health Project Manager, HFD-570
Division of Pulmonary and Allergy Products

Subject: **Request for Clinical Site Inspections**
NDA 22-124
Altana Inc.
Ciclesonide Nasal Spray

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
(b) (4)			
Site 3872 Jeffrey Wald, MD 8675 College Boulevard, Suite 200 Overland Park, KS 66210	M1-417	16	Seasonal Allergic Rhinitis
Site 4777 Investigator: William W. Storms, MD 1625 Medical Center Point, Suite 190 Colorado Springs, CO 80907	M1-417	18	Seasonal Allergic Rhinitis

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site 3482 Investigator: Ita Tripathy, MD Clinical Research of the Ozarks, Inc 509 East 10th Street Rolla, MO 65401	M1-417	18	Seasonal Allergic Rhinitis

Additional Comment:

We pointed out several hard to interpret entries for the morning nasal score. There are also afternoon scores that are difficult to interpret. For example, at Site 5205 2 subjects have entries timed close to noon (Subject 7780, entry 22880 and 22888; Subject 7930, entry 25495 and 25498). Please identify if these values were included in the analysis as afternoon or morning values.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) October 5, 2007. We intend to issue an action letter on this application by (division action goal date) October 23, 2007. The PDUFA due date for this application is November 23, 2007.

Should you require any additional information, please contact Colette Jackson at 301-796-1230.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-124

INFORMATION REQUEST LETTER

Altana Pharma US, Inc.
210 Park Avenue
Florham Park, NJ 07932

Attention: Cheryl Czachorowski
Director, Regulatory Affairs

Dear Ms. Czachorowski:

Please refer to your May 24, 2007, resubmission to your new drug application (NDA) for OMNARIS (ciclesonide) nasal spray.

We also refer to your submission dated June 14, 2007.

We are reviewing the Clinical section of your submission and have the following comments and requests for information. We request a prompt written response by July 27, 2007, in order to continue our evaluation of your NDA.

1. Provide the following information for Study M1-417:

   a. Submit documentation to validate the accuracy and reliability of the IVRS.

   b. Explain how the functioning of the IVRS was monitored in this study:

      i. Explain how often there were discrepancies between the hardcopy and IVRS and explain how such discrepancies were handled.

      ii. In Listing 16.2.4.8 several investigators noted that the caregiver claimed to have administered the medication correctly, but it was not recorded correctly in the IVRS. Provide information as to how often this occurred and explain how this discrepancy was handled for analysis.

      iii. The IVRS was supposed to accept entries only between the hours of 5:00 AM and noon and 5:00 PM and midnight. However, there are entries recorded early in the morning (between midnight and 1 AM). Explain how this happened and how the data were handled. Clarify if the score reported as the morning value was entered for that day or as the afternoon value for the previous day.

      iv. The AM evaluation was supposed to have been made upon arising, prior to any activity, and prior to taking study medication. Submit documentation on when the AM assessment was made.

c. Submit an analysis of the reflective TNSS using the data obtained from the hardcopy.

d. Sixty-six subjects are listed as taking a nasally inhaled corticosteroid on the Concomitant Medication summary (Table 14.1.4.1). Of these, 55 had a run-in period of less than 21 days (dataset …\tabulations\sv.xpt). On the other hand, the Protocol Violations listing (listing 16.2.4.11) includes only 7 cases of inappropriate nasal steroid use. Of the 7 cases listed, the commentary describes the violation as "30 days prior to B0" in 4 of the listings whereas it was described as "21 days before T0" in the remaining 3. Explain.

e. In Section 9.3.4 (pg 37/4502) you state that there were no specific protocol-defined withdrawal criteria. However in the disposition data set (…tabulations\ds.xpt) 5 subjects are listed as "Predefined discontinuation criterion fulfilled". Provide the predefined discontinuation criterion.

2. Provide the following information for Study M1-416:

Explain why so many of the baseline laboratory values in Study M1-416, including the AM cortisol, were above the normal range.

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

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Colette Jackson
7/12/2007 04:52:50 PM
Signed for S. Barnes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-124

ALTANA Pharma US, Inc.
220 Park Avenue
Florham Park, New Jersey 07932

Attention: Cheryl Czachorowski
Director, Regulatory Affairs

Dear Ms. Czachorowski:

We acknowledge receipt on May 24, 2007, of your May 24, 2007, resubmission to your new drug application for OMNARIS (ciclesonide) Nasal Spray.

We consider this a complete, class 2 response to our October 20, 2006, action letter. Therefore, the user fee goal date is November 24, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request within this application for a partial waiver of pediatric studies. We have reviewed your partial waiver request and agree that a waiver is justified only for pediatric studies in patients less than 2 years of age for ciclesonide since the disease does not exist or is difficult to diagnose in children of this age range.

We note that you have submitted pediatric studies for patients (b)(4) through 16 years of age with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury

7/3/2007 03:59:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug, Marketing, Advertising and Communication (DDMAC)
WO Bldg 22 Rm. 1400

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 26, 2007		22-124	N	May 24, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
OMNARIS (ciclesonide)	Standard	Pro-corticosteroid	September 7, 2007

NAME OF FIRM: ALTANA Pharma

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE—NDA MEETING
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II. BIOMETRICS

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☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for an evaluation and review of the package insert and patient instructions for use for OMNARIS (ciclesonide).
The labeling is being updated to include information for patients (ti 11 years of age.
This submission is electronic only and is located in the EDR in the submission dated May 24, 2007.

PDUFA DATE: November 23, 2007

CC:
Archival NDA 22-124
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Colette Jackson
6/26/2007 05:27:01 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: **March 5, 2007**

To: **Cheryl Czachorowski** **Director, Regulatory Affairs**	**From:** Carol Hill, M.S. Regulatory Project Manager
Company: **Altana Pharma**	Division of Pulmonary and Allergy Products
Fax number: 973-236-1695	**Fax number:** 301-796-9728
Phone number: 973-514-4271	**Phone number:** 301-796-1226

Subject: **NDA 22-124 – Comments regarding submission dated December 1, 2006**

Total no. of pages including cover: **5**

Comments:

Document to be mailed: ☐ **YES** ☑ **NO**

NDA 22-124
Altana Pharma
Omnaris (ciclesonide) Nasal Spray

We have completed our review of your submission dated December 1, 2006. Below you will find the questions contained in that submission along with our responses to each.

Question 1 - Content of Complete Response / Module 5 Clinical Study Reports
Does the Division agree to the inclusion and review of new onset of action data within this Complete Response for the purpose of a labeling change for OMNARIS (ciclesonide) Nasal Spray?

Response
No, we do not agree. The patient population for NDA 22-124 is patients under 12 years of age and the onset of action study was performed in patients 18 and older. You will need to submit a prior approval labeling supplement to NDA 22-004 with the onset of action data.

Question 2 - Cross-Reference Approach to Other Relevant Final Clinical Study Reports
Does the FDA agree with the approach to cross-referencing the studies M1-403 and M1-405?

Response
Cross-referencing studies M1-403 and M1-405 is acceptable.

Question 3 – Approach to Pediatric Integrated Summary of Safety (ISS)
Does the Division agree with the proposed content and approach to the integration plan for the ISS?

Response
We agree with the inclusion of studies M1-403 and M1-405 in the ISS. However, some consideration should be given to the effect of the studies' varying duration on the incidence of adverse events.

Question 4 – Content of Safety Update Report
Does the Division agree with the overall content and coverage period planned for the Safety Update Report?

Response
The plan is acceptable.

Question 5 – Datasets for Clinical Study Reports
Does the Division agree with this approach?

Response
See response to Question 7

Question 6 – Patient Profiles
Does the Agency agree with a waiver for patient profiles?

Response
See the response to Question 7.

Question 7 – Case Report Forms
Does the Agency agree with this approach?

Response
The plan is acceptable.

Question 8 – Nonclinical Information
Does the Division agree with the approach to the submission of Non-clinical Information?

Response
The plan to include in the Safety Update a 13-week juvenile rat inhalation study and a pharmacokinetic study in pregnant rats appears to be reasonable.

Question 9 – Module 1 Information
Does the Division agree with this approach?

Response
The approach is acceptable.

Question 10 – Labeling
Does the Division agree with the content, format and submission approach of the labeling?

Response
We agree that you do not need to include an SPL version in the complete response, but you should be prepared to submit the labeling in SPL prior to approval.

Question 11 – Regulatory Procedure associated with the Complete Response to NDA 22-124 and Labeling Supplement to NDA 22-004

Does the Division agree with the procedural approach to submissions associated with the Complete Response to pending NDA 22-124 (pediatric (b) (4) to 11 years of age) and the Labeling Supplement to approved NDA 22-004 (adolescent/adults 12 years and older)?

Response

(b) (4)

Question 12 – Proposed Table of Contents

Does the Division agree with the proposed content of the location of documents intended for inclusion with the Complete Response?

Response

The table of contents is acceptable.

If you have any questions, contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

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/s/

Carol F. Hill
3/5/2007 12:31:57 PM
CSO