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APPLICATION NUMBER:

202129Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 202,129 (Ciclesonide HFA 134a Nasal Spray)
Submissions dated March 19 and June 23, 2011, respectively

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
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DATE: December 7, 2011

I concur with the conclusions and recommendations of Dr. Luqi Pei's Review dated August 4, 2011. The review recommends approval of the application from the nonclinical perspective.

The sponsor has proposed to register Ciclesonide HFA nasal spray as a therapy for seasonal and perennial allergic rhinitis. This will be the first HFA-based nasal spray. (b) (4) The Agency has also approved an aqueous ciclesonide nasal spray (Omnaris™) for the indication of allergic rhinitis from the same sponsor.

The formulation of the to-be-marketed product contains ciclesonide, HFA 134a (b) (4) and ethanol (b) (4) The formulation was evaluated in the nonclinical program to assess potential local toxicity in the nasal cavity and sinuses. There was no significant evidence of local toxicity in studies using rats and dogs with treatment duration ranging from 28 to 90 days. See Dr. Pei's Review for further details.

There were no issues for impurities, extractables, and leachables (b) (4)

Dr. Pei's Review makes recommendations for changes in the product labeling in Sections 8.1 and (b) (4)

There are no outstanding PharmTox issues.

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/s/

TIMOTHY W ROBISON
12/07/2011

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 202,129
Supporting document/s:	Sequences 0000 and 0004
Applicant's letter date:	March 18 and June 23, 2011
CDER stamp date:	March 21 and June 23, 2011
Product:	Ciclesonide HFA 134a Nasal Spray
Indication:	Rhinitis
Applicant:	Nycomed Inc.
Review Division:	Pulmonary, Allergy and Rheumatology
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Timothy Robison, Ph.D.
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

This application (NDA 202,129) proposes to register ciclesonide HFA nasal spray for allergic rhinitis in patients 12 years and older. This is a 505(b)(1) application that uses NDAs 21-658, 22-004 and 22-124 as references. Nycomed is the owner of all three NDAs.

Ciclesonide is approved and currently marketed for both asthma and allergic rhinitis indications. There are currently 2 marketed ciclesonide products: Alvesco® Inhalation Aerosol (NDA 21-658) and Omnaris AQ Nasal Spray (NDAs 22-004 and 22-124). Alvesco® is a HFA 134a formulation indicated for asthma in patients 12 years and older (approved on January 10, 2008). Omnaris AQ is an aqueous formulation indicated for allergic rhinitis in patients 6 years of age and older (approved on October 26, 2006 and November 21, 2007, respectively). The maximum recommended human daily doses of ciclesonide in adults are 640 and 200 μg/day for asthma and allergic rhinitis indications, respectively.

Ciclesonide HFA Nasal Spray (NDA 202,129) and Alvesco (b) (4) consists of HFA-134a and ethanol (b) (4). Each actuation of the to-be-marketed product and Alvesco will release 50 and 80-μg ciclesonide from the actuator valve, respectively. Also, both Omnaris and the to-be-marketed product releases 50-μg ciclesonide from the valve, the to-be-marketed product will release 37-μg ciclesonide from its mouth piece. This modification results in a lower human dosage for the to-be-marketed product: 74 μg/day in adults.

The developmental program in support of NDA 202,129 was done under IND 74,674. The Division of Pulmonary, Allergy and Rheumatology Product (DPARP) and Nycomed held a number of meetings to discuss the developmental program of the product. The nonclinical development requirements were discussed in the 16-OCT-2006 pre-IND meeting. It was agreed that no additional nonclinical studies will be needed for the registration of HFA nasal spray formulation.

The applicant resubmitted all nonclinical data in support of the registration of Alvesco and Omnaris AQ. The applicant also submitted the following new nonclinical data: five pharmacokinetic studies and three toxicology studies. The pharmacokinetic data included two studies of the HPLC-MS/MS method validation and three in vitro metabolism studies of human nasal tissues, cells or CYP enzymes. The toxicology data included two 13-week inhalation toxicity studies in juvenile rats and dogs and a dose range finding study for the 13-wk study in rats. These studies will not be reviewed because they are irrelevant to the safety evaluation of the to-be-marketed product.

1.2 Brief Discussion of Nonclinical Findings

No new, significant nonclinical data were submitted. Data pivotal to the nonclinical safety evaluation of nasal ciclesonide have been submitted to and reviewed by the Agency in reference NDA applications. These applications are NDAs 21-658

(Alvesco Inhalation aerosol), 22-004 (Omnaris AQ Nasal Spray), and 22-124 (Omnaris AQ Nasal Spray). Significant nonclinical findings have been summarized in nonclinical reviews and Approval Letters of these NDAs. The nonclinical reviews were completed by Dr. Huiqing Hao on September 30, 2004 in NDA 21-658, August 30, 2006 in NDA 22-004, and October 29, 2007 in NDA 22-124, respectively. The Approval Letters were issued on 10-JAN-2008 for NDA 21-658, 20-OCT-2006 for NDA 21-658, and 21-NOV-2007 for NDA 22-004, respectively. The following summary information is based on the previous nonclinical reviews and the Approval Letters for reference NDAs. See the above documents for additional information.

Pharmacology: Ciclesonide is a pro-drug of des-ciclesonide (or RM1), a pharmacologically active metabolite. The precise mechanisms of corticosteroid action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of allergic rhinitis. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the allergic inflammation.

Pharmacokinetic and Toxicokinetics: Oral bioavailability of ciclesonide is less than 6% in most species. Both ciclesonide and RM-1 have a large volume of distribution (4-6 L/kg in rats, mice and dogs). The t½ of ciclesonide was 1 hour in rats and mice while t½ of RM-1 was 2.4 to 7 hours in rats, mice, rabbits, and dogs. Systemically absorbed ciclesonide is rapidly de-esterified to active metabolite RM-1 that is further metabolized to several compounds. The primary enzyme responsible for metabolism of RM-1 is CYP 3A4. All of the metabolites of RM-1 including fatty acid conjugates of RM-1 had much less pharmacological activity than RM-1 and were considered inactive. In human and animal nasal mucosa, ciclesonide is metabolized to RM-1 and subsequently to fatty acid conjugates of RM-1. The rate of metabolism for ciclesonide in the nasal mucosa are similar among the animal species studied (ciclesonide t½ = 1-2 hours in nasal mucosa homogenates from rats, rabbits, guinea pigs and dogs). The major systemic elimination pathway is bile and feces (80%). Both ciclesonide and RM-1 were approximately 99% plasma protein bound in all species studied. No drug accumulation was noted.

Toxicology: Complete toxicology programs have been conducted with ciclesonide to support clinical administration by the inhalation and intranasal routes. Ciclesonide possesses a toxicological profile typical of glucocorticoids. Major toxicity observed in animal studies include immunosuppression, decreased body weights, slight increases in blood triglyceride and cholesterol levels, adrenal suppression, and lymphoid tissue atrophy.

Genetic toxicity: Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the in vivo mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings.

Carcinogenicity: Ciclesonide demonstrated no carcinogenic potential in 2-year studies at oral doses up to 900 µg/kg/day in mice or inhalation doses up to 193 µg/kg/day in rats, respectively.

Impairment on Fertility: Ciclesonide did not impair fertility in male and female rats at oral doses up to 900 μg/kg/day in a reproductive study.

Teratogenic Effects: Pregnancy Category C. Oral administration of ciclesonide up to 900 μg/kg/day produced no teratogenicity or other fetal effects in rats, but subcutaneous administration of ciclesonide in rabbits at 5 μg/kg/day or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 μg/kg.

Overall, ciclesonide is non-genotoxic and non-carcinogenic. The drug has a Pregnancy C categorization for its teratogenic effects.

1.3 Recommendations

1.3.1 Approvability

Approval of the application is recommended from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Edits to Sections 8.1 (Pregnancy) and 13 (nonclinical toxicology) of the proposed labeling of the ciclesonide HFA nasal spray are recommended. No edits are recommended for sections 8.3 (Nursing mother), 10 (Overdosage), and 12.1 (mechanism of action). See Labeling Review section (page 11) for discussions regarding the recommended edits. Below is recommended text for sections 8.1 and 13.[1]

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. TRADENAME Nasal Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Oral administration of ciclesonide in rats at approximately 120 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mcg/m^2 basis at a maternal dose of 900 mcg/kg/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at similar to MRHDID (on a mcg/m^2 basis at a maternal dose of 5 mcg/kg/day) produced fetal

[1] The applicant submitted two versions of draft package inserts (or labeling). They were submitted on March 18 and June 23, 2011, respectively. Their nonclinical sections, however, were identical.

toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1/4 of the MRHDID in adults (on a mcg/m^2 basis at a maternal dose of 1 mcg/kg/day).

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in mice in a study of oral doses up to 900 mcg/kg (approximately 60 times the maximum recommended human daily intranasal dose (MRHDID) in adults based on mcg/m^2/day) in mice for 104 weeks, or in a study in rats of inhalation doses up to 193 mcg/kg (approximately 25 times MRHDID in adults based on mcg/m^2/day) for 104 weeks.

Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings.

No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 120 times MRHDID in adults based on mcg/m^2/day).

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 1418-82-1

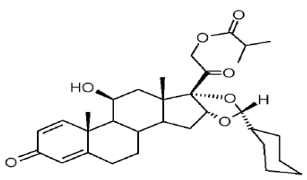
Generic Name: Ciclesonide HFA nasal spray

Code Name: BYK 20426, B9207-15

Chemical Name: Pregna-1,4-diene-3,20-dione, 16, 17-{[R-cyclohexylmethylene]-bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11b, 16a)-

Molecular Formula/Molecular Weight: $C_{32}H_{44}O_7$, 540.7

Structure or Biochemical Description:



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

Product	IND/NDA	Ciclesonide (µg/day)	Indication	Population	Date of Approval
Cicles. HFA MDI	I53,391	-	Asthma	≥12 yr	-
Cicles. AQ NS	I65,488	-	Rhinitis	-	-
Cicles. HFA NS	I74,674	-	Rhinitis	≥12 yr	-
Alvesco HFA MDI	N21-658	640	Asthma	≥12 yr	1/10/08
Omnaris AQ NS	N22-004	200	Rhinitis	≥12 yr	10/20/06
Omnaris AQ NS	N22-124	200	Rhinitis	≥ 6 yr	11/21/07

The following DMFs were cited in the nonclinical review completed by Dr. Huiqing Hao on August 30, 2006 in NDA 22-004: DMFs (b) (4)

2.3 Drug Formulation

Two types of canisters are being developed. A canister may be filled either 30 or 60 actuations. The composition of the formulation of the two canisters is identical (Table 1). Each actuation delivers 50 and 37 µg of ciclesonide from ex-valve and the mouth piece, respectively.

Table 1: Composition of the Ciclesonide HFA Nasal Spray

Ingredient	Concentration (%, w/v)	mg/actuation		Function
		Ex-valve	Ex-mouth piece	
Ciclesonide	(b) (4)	0.050	0.037	API
Alcohol (dehydrated)		(b) (4)		(b) (4)
HFA 134a				Propellant
Total				

a, NA = not available.

2.4 Comments on Novel Excipients

No novel excipient is presen (b) (4) in the approved and currently marketed drug product (Nasacort HFA Nasal Aerosol, NDA 20-784). The applicant, however, has qualified an alcohol concentration of (b) (4) in its nonclinical program. See Integrated Summary and Safety Evaluation section for the qualification information.

2.5 Comments on Impurities/Degradants of Concern

None. (b) (4) Any impurities present in the to-be-marketed products have been considered acceptable (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Ciclesonide Nasal Aerosol is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The recommended dose of ciclesonide dose is 74 μg/day (37 mcg/actuation, 1 actuation/nostril/day).

2.7 Regulatory Background

Application NDA 202,129 is a 505(b)(1) application proposing an indication of allergic rhinitis in adults. It uses Alvesco® Inhalation Aerosol (NDAs 21-658) and Omnaris AQ Nasal Spray (22-004 and 22-124) as references. The active pharmaceutical ingredient is ciclesonide in each of these applications. Nycomed is the owner of Alvesco, Omnaris and the to-be-marketed product.

Both Alvesco and Omnaris are currently on the market. Approved on January 10, 2008, Alvesco was indicated for asthma in patients 12 years and older. Approved on October 26, 2006 and November 21, 2007, respectively, Omnaris AQ Nasal Spray was approved for the rhinitis indication in adult and pediatric (≥ 6 yrs) populations. (b) (4)

NDA 202,129 was supported by IND 74,674. The Division of Pulmonary, Allergy and Rheumatology Product (DPARP) and Nycomed held a number of meetings to discuss the developmental program of the product. Nonclinically, it was agreed in the 16-OCT-2006 pre-IND meeting that no additional nonclinical studies will be needed for the registration of HFA nasal spray formulation.

3 Studies Submitted

3.1 Studies Reviewed

None. All the studies except for those listed in Table 1 in Section 3.2 - Studies Not Reviewed have been submitted and reviewed previously. See nonclinical reviews completed by Dr. Huiqing Hao on September 30, 2004 in NDA 21-658, August 30, 2006 in NDA 22-004, and October 29, 2007 in NDA 22-124 for reviews and evaluations of these studies.

3.2 Studies Not Reviewed

Studies listed in Table 2 (next page) are not reviewed because they are either irrelevant or non-pivotal to the nonclinical safety evaluations of the current drug products. The to-be-marketed products will be indicated for patients 12 years and older. The newly submitted toxicology studies were done in juvenile animals. Studies in juvenile animals are not needed for the nonclinical safety evaluations of drugs indicated in 12 years of age and older.

Table 2: Submitted but NOT Reviewed Studies

	Study #	Description	Ciclesonide [µg/kg/day]	Section
MDPK	93/2005	HPLC-MS/MS method validation	In vitro	4.2.2.4
	140/2007	Metabolism by human NEC	In vitro	4.2.2.4
	141/2007	Reversibility of metabolism by nasal epithelial cells	In vitro	4.2.2.4
	401/2007	HPLC-MS/MS method validation	In vitro	4.2.2.4
	493/2007	In vitro human CYP metabolism	In vitro	4.2.2.4
TOX	19/2007	19-d IH Tox in juvenile rats	0, 8.3, 25.2, 80.8	4.2.3.5.4
	26/2008	13-wk IH Tox in juvenile dogs	0, 29, 85, 175	4.2.3.5.4
	128/2008	13-wk IH Tox in juvenile rats	0, 0 (V), 5.5, 17.9, 48.9	4.2.3.5.4

3.3 Previous Reviews Referenced

This review references to nonclinical reviews completed by Dr. Huiqing Hao on September 30, 2004 in NDA 21-658, August 30, 2006 in NDA 22-004, October 29, 2007 in NDA 22-124, and December 21, 2006 in IND 74,674, respectively.

4 Pharmacology

Not applicable because no new data were submitted.

5 Pharmacokinetics and Toxicokinetics

Not applicable because no significant, new data were submitted.

6 General Toxicology

Not applicable because no data were submitted.

7 Genetic Toxicology

Not applicable because no data were submitted.

8 Carcinogenicity

Not applicable because no data were submitted.

9 Reproductive and Developmental Toxicology

Not applicable because no data were submitted.

10 Special Toxicology Studies

No new, pivotal data relevant to the nonclinical safety evaluations of the current application were submitted. The current application submitted 3 toxicology study reports that had not been submitted previously. These studies (Studies 26/2008,

128/2008 and 19/2007) evaluated the effect of ciclesonide HFA134a formulation in juvenile rats and dogs. Studies 26/2008 and 128/2008 are 13-week inhalation toxicity studies in rats and dogs (one each). Study 26/2008 is a dose range-finding study in rats. These studies will not be reviewed because they dot provide relevant information to the nonclinical safety evaluation of the current application: patients 12 years of age and older. Also, a preliminary review of the newly submitted studies revealed no new safety signals were identified.

11 Integrated Summary and Safety Evaluation

This application (NDA 202,129) has submitted adequate nonclinical information to support the safety of ciclesonide HFA nasal spray. Nycomed proposed to register ciclesonide HFA nasal spray as a therapy for allergic rhinitis. The Agency has approved ciclesonide for the allergic rhinitis indication and the formulation for asthma indication previously in reference NDAs. The formulation was also studied in a 13-week head-only inhalation toxicity study in dogs. Approval of the application is recommended from the nonclinical perspective.

Nycomed in NDA 202,129 proposes to register ciclesonide HFA nasal spray for allergic rhinitis in patients 12 years and older. Nycomed proposed to market two types of canisters: 30 or 60 actuations/canister. The formulation of the two canisters is also identical. (b) (4) One actuation of both products delivers 50 and 37-μg ciclesonide from the valve and mouth piece of the device, respectively. The maximum recommended human dose (MRHD) of ciclesonide in NDA 202,129 will be 74 μg/day (37 μg/actuation, 2 actions each nostril).

Nycomed is referencing two previously approved and currently marketed products to support the to-be-marketed products (NDA 202,129.) The reference products are Alvesco® Inhalation Aerosol (NDA 21-658) and Omnaris AQ Nasal Spray (NDAs 22-004 and 22-124). Table 3 (below) summarizes the characteristics of the products of interest. Alvesco® is a HFA 134a formulation indicated for asthma in patients 12 years and older (approved on January 10, 2008). Omnaris AQ is an aqueous formulation indicated for allergic rhinitis in patients 6 years of age and older (approved on October 26, 2006 and November 21, 2007, respectively). The MRHD of ciclesonide is 640 and 200 μg/day for Alvesco and Omnaris AQ, respectively.

Table 3: Major Characteristics of Ciclesonide Products

NDA No.	21-658	22-004	22-124	202,129
Product Name	Alvesco	Omnaris	Omnaris	TBD
Formulation	HFA 134a [a]	Aqueous	Aqueous	HFA 134a [a]
Indication	Asthma	Rhinitis	Rhinitis	Rhinitis
Patient age (year)	≤ 12	≤ 12	≤ 6	≤ 12
MRHD (μg/day) [b]	640	200	200	74

a. The vehicle consists of HFA134a and ethanol (b) (4)
b. MRHD, the maximum recommended human daily doses.

There are major commonalities and differences among the to-be-marketed products, Alvesco and Omnaris. The commonalties are: (b) (4)

(b) (4) the to-be-marketed products and Omnaris have the same indication. The difference exists in the clinical dose of the products: the MRHD is 640, 200 and 74 μg/day for Alvesco, Omnaris AQ, and the to-be-marketed products, respectively.

Nycomed resubmitted the nonclinical study reports that the Agency had previously reviewed. See nonclinical reviews completed by Dr. Huiqing Hao on September 30, 2004 in NDA 21-658, August 30, 2006 in NDA 22-004, and October 29, 2007 in NDA 22-124 for detailed review. There is no need to reevaluate the previously reviewed data.

The Agency has approved ciclesonide in the proposed formulation for asthma indication and an aqueous formulation for rhinitis indication. Nonclinical safety evaluation of nasal and inhaled ciclesonide has been completed in the reference NDAs. Significant nonclinical findings have been described in the labels of the reference products. As eluded to earlier, the MRHD of ciclesonide for the to-be-marketed product is smaller than that the Agency has determined to be safe.

The formulation of to-be-marketed product consists of ciclesonide, HFA 134a (b) (4) and ethanol (b) (4). The formulation was evaluated in the nonclinical program. The evaluation included 28-day inhalation toxicity studies in rats and dogs (one each, Reports 92E/97 and 103/97) and a 90-day inhalation study in dogs (Report 273/98). These studies were reviewed by Dr. Satish Tripathi on November 5, 1997 and Dr. Huiqing Hao on December 12, 2001 in IND 53,391, respectively. See Attachments 3 and 8 in the nonclinical review completed by Dr. Huiqing Hao on September 30, 2004 in NDA 21-658 for the reviews. Dr. Hao's review concluded that the studies did not reveal any findings of nonclinical safety concerns in the nasal cavity. Briefly, dogs were treated by head-only inhalation with the testing vehicle aerosol containing up to 15 μg/L ciclesonide for 90 days. Also, DPARP determined in the 16-OCT-2006 pre-IND meeting that no additional nonclinical studies will be needed for the registration of FHA nasal spray formulation. The nonclinical safety of the to-be-marketed products has been established.

Overall, Nycomed has satisfied the nonclinical requirements for registration of the proposed product in NDA 202,129. The review recommends approval of the application from the nonclinical perspective, pending labeling review.

LABELING REVIEW

This labeling review uses the most recent approved and the PLR-(product labeling rule) compliant labeling of currently marketed ciclesonide products as the basis of the recommended labeling for the to-be-marketed products. Table 4 lists the approved and currently marketed products. They are Alvesco Inhalation Aerosol and Omnaris AQ Nasal Spray indicated for asthma and rhinitis, respectively.

Table 4: Approved and Currently Marketed Ciclesonide products

Product	NDA#	Ciclesonide (μg/day)	Indication	Popu-lation	Date of Approval	
					Product	Label revision
Alvesco HFA MDI	N21-658	640	Asthma	≥12 yr	1/10/08	12/22/08
Omnaris AQ NS	N22-004	200	Rhinitis	≥12 yr	10/20/06	5/7/10
Omnaris AQ NS	N22-124	200	Rhinitis	≥ 6 yr	11/21/07	11/21/07

Both Alvesco and Omnaris labeling are relevant to the review of the proposed label of the to-be-marketed products. This is due to commonalities between these products: indication [redacted] (b) (4) with Omnaris [redacted] (b) (4). However, there are also differences between Alvesco, Omnaris and the to-be-marketed products. The most significant difference is the recommended clinical dose for patients 12 years of age and older. The maximum recommended clinical dose in humans is 640, 200 and 74 μg/day for Alvesco, Omnaris and the to-be-marketed products, respectively.

Table 5 presents the pregnancy section of the labeling of the currently marketed Alvesco and Omnaris products. Both contents and format of the two labels differ. The Omnaris label did not describe the nonclinical findings in detail while the Alvesco label did. Detailed description of nonclinical findings in the Omnaris label was moved to Section 13.2 – animal reproductive toxicity.

Table 5: Text of Pregnancy Section Alvesco and Omnaris of Labels

Alvesco (NDA 21-658) Indicated for Asthma Approved on December 22, 2008	Omnaris (NDA 22-004) Indicated for Rhinitis Approved on May 7, 2010
8.1 Pregnancy Teratogenic Effects: Pregnancy Category C Oral administration of ciclesonide in rats up to 900 mcg/kg/day (approximately 10 times the maximum human daily inhalation dose based on mcg/m^2/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg/day (less than the maximum human daily inhalation dose based on mcg/m^2/day) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily inhalation dose based on mcg/m^2). There are no adequate and well-controlled studies in pregnant women. ALVESCO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy. Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.	**8.1 Pregnancy** Teratogenic Effects: Pregnancy Category C There are no adequate and well-controlled studies in pregnant women. Omnaris should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy. Oral administration of ciclesonide in rats at approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2 produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at less than the maximum human daily intranasal dose in adults based on mcg/m^2 produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects [*see Animal Toxicology and Pharmacology (13.2)*]. Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

The Agency recently determined that the Alvesco format is preferred because it conveys information more concisely. Based on the above discussions, the review concludes that the label of the to-be-marketed product should use the format of Alvesco label.

The to-be-marketed product will have a new recommended clinical dose. The new dose necessitates calculations of new dose ratios between animals and humans for the to-be-marketed products. Also, DPARP recently decided to use a 60-kg body weight for adult population (vs 50-kg/person previously). Table 6 presents the estimated dose ratios for the labeling review and basis of obtaining these dose ratios. Animal dose levels are obtained from the proposed labels and the labels of approved products (Alvesco and Omnaris).

Table 6: **Animal-to-Human Dose Ratios for Labeling**

						Animal-to-Human Ratio [a]	
Section	Description	Species	mg/kg	Km	Mg/m^2	Calculated [b]	Suggested [c]
8.1	Pregnancy	Rat	0.9	6	5.4	118.3	120
		Rabbit	0.005	12	0.06	1.3	1
13.1	Carcinogenicity	Mouse	0.9	3	2.7	59.2	60
		Rat	0.193	6	1.16	25.4	25
13.1	Fertility	Rat	0.9	6	18	118.3	120

a. On a mg/m^2 basis.
b. Calculated based on human exposure of 0.04563 mg/m^2/day (0.074 mg/day ÷ 60 (kg) x 37 (kg/m^2) = 0.04563 mg/m^2/day).
c. Rounded to.

The following sections of the product labeling are relevant to the nonclinical discipline: 8.1 - Pregnancy, 10 - Overdosage, 12.1 - Mechanism of Action, and 13 – Nonclinical Toxicology. The nonclinical sections of the approved label of Alvesco were based on the review completed by Dr. Huiqing Hao on December 20, 2007 in NDA 21-658. The section below discusses each nonclinical sections of the labeling of the to-be-marketed products.

PREGNANCY

The Proposed text for 8.1 – Pregnancy of the to-be-marketed product is presented below. The proposed text is the same as that of label of Omnaris in adult population which was approved on May 7, 2010 (NDA 22-004) except for the dose ratios between animals and humans. The recommended text is generally the same as that of Alvesco approved on December 22, 2008. Contents of Paragraphs 1 and 3 are identical to that of Omnaris labeling and no discussions are needed. The review recommends revising paragraph 2 as discussed later.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. TRADENAME Nasal Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids

since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Oral administration of ciclesonide in rats at approximately (b) (4) 120 times the maximum recommended human daily intranasal dose (MRHDID) in adults (b) (4) (on a mcg/m^2 basis at a maternal dose of 900 mcg/kg/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at (b) (4) (on a mcg/m basis at a maternal dose of 5 mcg/kg/day) produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at (b) (4) 1/4 of the MRHDID in adults (on a mcg/m^2 basis at a maternal dose of 1 mcg/kg/day) (b) (4)

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

Section 8.3 – Nursing mothers also refers to nonclinical data. The proposed text for this section is acceptable because it is identical to that of Alvesco labeling approved on January 10, 2008 in NDA 21-658. The proposed text for Section 8.3 is as following:

8.3 Nursing Mothers

It is not known if ciclesonide is excreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal but detectable levels of ciclesonide were recovered in milk. Caution should be used when TRADENAME Nasal Aerosol is administered to nursing women.

OVERDOSAGE

The review recommends no edits to the Overdosage section of the proposed label from the nonclinical perspective. Table 6 presents the text of the labels for Omnaris and the proposed for the to-be-marketed products. The Agency recently determined that the Overdosage section should generally refrain from discussing nonclinical data. The clinical section will be reviewed by the medical review team.

Table 6: Text of Overdosage Sections of Omnaris and Proposed Labels

Omnaris (NDA 21-658) Indicated for Asthma Approved on May 7, 2010	To-be-marketed Product (NDA 202,129) Indicated for Rhinitis In review
Chronic overdosage may result in signs/ symptoms of hypercorticism *[see Warnings and Precautions (5.5)]*. There are no data available on the effects of acute or chronic Overdosage with Omonaris Nasal Spray.	Chronic overdosage may result in signs or symptoms of hypercorticism [*see WARNINGS AND PRECAUTIONS (5.4)*]. There are no data on the effects of acute or chronic overdosage with TRADENAME Nasal Aerosol. Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical trials (with dosages of up to 282 mcg/day for up to 6 weeks [4 times the maximum recommended dose]), overdose is unlikely to require any therapy other than observation. TRADENAME Nasal Aerosol was well tolerated following nasal inhalation of doses up to 282 mcg in PAR subjects for up to 6 weeks and doses of up to 148 mcg in PAR subjects for up to 26 weeks. A single oral dose of up to 10 mg of ciclesonide in healthy subjects was well tolerated and serum cortisol levels were virtually unchanged in comparison with placebo treatment. Acute overdose with the intranasal aerosol dosage form is unlikely since one 60 count canister of TRADENAME Nasal Aerosol 37 mcg contains approximately 5 mg of ciclesonide.

MECHANISM OF ACTION

No comments on the proposed text for Section 12.1 - Mechanism of Action are needed. The proposed text is identical to what has been approved in the Omnaris Label. There is no new nonclinical data that warrant any changes of the previously approved text from the nonclinical perspective. The proposed label is, therefore, acceptable. Below is the proposed text:

> **"12.1 Mechanism of Action**
>
> Ciclesonide is a pro-drug that is enzymatically hydrolyzed to a pharmacologically active metabolite, C21-desisobutyryl-ciclesonide (des-ciclesonide or RM1) following intranasal application. Des-ciclesonide has anti-inflammatory activity with affinity for the glucocorticoid receptor that is 120 times higher than the parent compound.
>
> The precise mechanism through which ciclesonide affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic inflammation."

NONCLINCIAL TOXICOLOGY

(b) (4)

Minor edits to Section 13.1 are recommended.

(b) (4)

13.1 Carcinogenesis, mutagenesis, impairment of fertility

The proposed text for Section 13.1 – carcinogenesis, mutagenesis and impairment of fertility is generally acceptable. Table 7 (next page) presents the text of the labels for Alvesco and Omnaris, and the proposed for the to-be-marketed products.

Table 7: Carcinogenesis Section of Ciclesonide Product Labels

Alvesco (NDA 21-658) Approved on January 10, 2008	Omnaris (NDA 22-004) [b] Approved on October 26, 2006	Ciclesonide NS (202,129) Proposed on March 18, 2011
13. 1 Carcinogenesis, Mutagenesis, Impairment of Fertility Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg/day (approximately 6 times the maximum human daily inhalation dose based on mcg/m^2/day) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg/day (approximately 2 times the maximum human daily inhalation dose based on mcg/m^2/day) in rats for 104 weeks. … [a] No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 10 times the maximum human daily inhalation dose based on mcg/m^2/day).	**Carcinogenesis, Mutagenesis, Impairment of Fertility** Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 times the maximum human daily intranasal dose in adults based on mcg/m2) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 times the maximum human daily intranasal dose in adults based on mcg/m^2) in rats for 104 weeks. … No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m^2).	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Ciclesonide demonstrated no carcinogenic potential in mice in a study of oral doses up to 900 mcg/kg (approximately 50 times the maximum human daily intranasal dose in adults and adolescents ≥ 12 years of age based on mcg/m^2/day) in mice for 104 weeks, nor in a study in rats of inhalation doses up to 193 mcg/kg (approximately 23 times the maximum human daily intranasal dose in adults and adolescents ≥ 12 years of age based on mcg/m^2/day) for 104 weeks. … No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 108 times the maximum human daily intranasal dose in adults based on mcg/m^2/day).

a, Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an in vitro micronucleus test. However, ciclesonide was clastogenic in the in vivo mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings.

b. Three versions of Omnaris labels have been approved. They were approved on October 20, 2006, November 21, 2007 and May 7, 2010, respectively. The 20-OCT-2006 version was for adult patients only while the 21-NOV-2007 and 07-MAY-2010 versions were for both adult and pediatric patients.

Because both the 20-OCT-2006 version and the to-be-marketed are for the same patient population, the review uses the 20-OCT-2006 version as a template.

As discussed earlier, ratio ratios between animals and humans should be revised. Below is the recommended edits to the proposed label. (b) (4) Below is the recommended edits to the proposed text of Section 13.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in mice in a study of oral doses up to 900 mcg/kg (approximately (b) (4) 60 times the maximum recommended human daily intranasal dose (MRHDID) in adults (b) (4) based on mcg/m^2/day) in mice for 104 weeks, or in a study in rats of inhalation doses up to 193 mcg/kg (approximately (b) (4) 25 times ~~the maximum human daily intranasal dose~~MRHDID in adults ~~and adolescents ≥ 12 years of age~~ based on mcg/m^2/day) for 104 weeks.

Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings.

No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately (b) (4) 120 times (b) (4) MRHDID in adults (b) (4) based on mcg/m /day).

(b) (4)

Luqi Pei, Ph.D.
Senior Pharmacologist

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

/s/

LUQI PEI
08/04/2011

TIMOTHY W ROBISON
08/04/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202,129 **Applicant:** Nycomed **Stamp Date:** March 21, 2011

Drug Name: Ciclesonide HFA nasal spray **NDA/BLA Type:** Original NDA

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		All studies pivotal to the nonclinical safety evaluation of the application have been previously submitted and reviewed in NDAs 21-658 and 22-004. See Note A of the table for the newly submitted studies.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. See comments in Item 1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. See comments in Item 1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. See comments in Item 1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		x	The to-be-marketed product (HFA 134a) is a reformation of Omnaris aqueous nasal spray (NDA 22-004). (b) (4) The to-be-marketed formulation is not considered a new one because there was adequate nonclinical characterization of the HFA formulation previously.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		The proposal labeling is in the PLR format and generally the same as the one recently approved by the Agency on May 7, 2010 in NDA 22-004. Few minor changes in text will be handled during the labeling review.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?	x		The drug is approved and currently marketed for the same route of the administration and same patient demographics.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. There is currently no OTC nasal spays of corticosteroids.

A. The newly submitted data include reports of five pharmacokinetic reports and three toxicology studies (Table 1, below). The pharmacokinetic reports included two studies of the HPLC-MS/MS method validation and three in vitro metabolism studies of human nasal tissues, cells or CYP enzymes. The toxicology data included two 13-week inhalation toxicity studies in juvenile rats and dogs and a dose range finding study for the 13-wk study in rats. These studies will not be reviewed because the use populations of the to-be-marketed product and reference product are identical: patients 12 years and older. Further, the PK studies provide no additional value to the nonclinical safety evaluation of the application.

Table 1: Newly Submitted Non-clinical Studies that will not be reviewed

MDPK	Study #	Description	Cicleosonide [µg/kg/day (Ac)]	Section
	93/2005	HPLC-MS/MS method valid.	In vitro	4.2.2.4
	140/2007	Metabolism by human NEC	In vitro	4.2.2.4
	141/2007	Reversibility of metabolism by nasal epithelial cells (NEC)	In vitro	4.2.2.4
	401/2007	HPLC-MS/MS method valid.	In vitro	4.2.2.4
	493/2007	In vitro human CYP metabolism	In vitro	4.2.2.4
TOX	19/2007	19-d IH Tox in juvenile rats	0, 8.3, 25.2, 80.8	4.2.3.5.4
	26/2008	13-wk IH Tox in juvenile dogs	0, 29, 85, 175	4.2.3.5.4
	128/2008	13-wk IH Tox in juvenile rats	0, 0 (V), 5.5, 17.9, 48.9	4.2.3.5.4

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES._____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Luqi Pei, Ph.D.	May 3, 2011
Reviewing Pharmacologist	Date
Timothy Robison, Ph.D.	May 3, 2011
Team Leader	Date

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

/s/

LUQI PEI
05/03/2011

TIMOTHY W ROBISON
05/03/2011
I concur