CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-124s000

PHARMACOLOGY REVIEW(S)

Supervisory Pharmacologist Review

NDA: 22-124 – Omnaris, Ciclesonide Nasal Spray
FROM: Timothy J. McGovern, Ph. D., Supervisory Pharmacologist
DATE: October 30, 2007

I concur with the recommendation by Dr. Huiqing Hao, the pharmacology/toxicology reviewer, that the pharmacology and toxicology of Omnaris, ciclesonide nasal spray, have been adequately studied and evaluated and that the drug product is approvable from a nonclinical standpoint (see review dated October 29, 2007). In regard to the nonclinical data, the application referenced much of the data generated by Aventis Pharmaceuticals for IND 53,391 and NDA 21-658, Alvesco ciclesonide inhalation solution, which is also considered to be approvable at this time. Altana obtained authorization to reference this data.

NDA 22-004 (Omnaris nasal spray) was previously approved in subjects 12 years and older. At the time of approval, the NDA (b) (4) between ages 12 and above (NDA 22-004) (b) (4) (the current NDA). At that time, NDA 22-124 was deemed Approvable (b) (4). No nonclinical deficiencies were noted. For both applications, the sponsor, in agreement with the Division, conducted an abbreviated intranasal toxicology program (described under general toxicology) designed to complement the previously conducted inhalation studies and to investigate the toxicity profile via the intranasal route of administration. These new studies revealed no new significant toxicities.

Pharmacology: The actions of ciclesonide as a pro-drug based on its major active metabolite (MR-1) activity were typical for its class and did not distinguish it from other glucocorticoids. Intranasal ciclesonide inhibited inhibited IL-1β-induced IL-8 release in human nasal epithelial cells and bronchial epithelial cells. In a guinea pig allergic rhinitis model, administration of ciclesonide prevented increase of nasal respiratory resistance and increase of eosinophils in nasal lavage fluid.

General toxicology: The nonclinical program for NDA 22-004 was abbreviated since the sponsor was authorized to reference the complete program for the inhalation route of administration under IND 53,391 and NDA 21-658 conducted by Aventis Pharmaceuticals. Altana conducted an intranasal toxicology program consisting of 14 and 28-day studies in rats and dogs and a 6-month dog study. The intranasal studies identified no local (intranasal) toxicities in rats (up to 429 mcg/kg or 7.7 mcg/cm^2 nasal surface area, 4 weeks). In dogs, nasal associated lymphoid tissue (NALT) atrophy was observed at an intranasal dose of 4800 mcg/day (21.8 mcg/cm^2 nasal surface area) at 4 weeks and 6 months duration of treatment. The no observed adverse effects levels (NOAELs) for the dog studies were 1200 mcg/day (5.5 mcg/cm^2 nasal surface area). On a mcg/cm^2 nasal surface area basis, the NOAELs in the rat and dog studies provided 6.2- and 4.3-fold safety margins, respectively, regarding local toxicities for the proposed human dose of 200 mcg/day (1.25 mcg/cm^2).

Systemic toxicities observed in the intranasal program were typical for glucocorticoids and were also reported in the inhalation program. The toxicities included decreased body weight (or body weight gain), increases in blood triglyceride and cholesterol levels, adrenal suppression and lymphoid tissue atrophy (thymus, spleen, lymph nodes and bronchus-associated lymphoid tissues). In addition to the typical glucocorticoid effects, testicular atrophy was observed in dogs following intranasal administration at a dose of 4800 mcg/day for 6 months duration. The systemic exposure at the NOAEL dose in this study (1200 mcg/dog/day) correlated with Cmax values of 334 and 295 pg/mL for ciclesonide and des-ciclesonide, respectively; AUC0-24h of 586 and 1284 pg.h/mL for ciclesonide and des-ceclesonide, respectively. Human serum levels were undetectable following 800 mcg/day intranasal administration in adults or pediatric subjects (lower quantitative limits of 25 pg/mL for ciclesonide and 10 pg/mL for des-ciclesonide). On a mcg/kg basis, the dog NOAEL of 1200 mcg/dog provides approximately a 30-fold safety margin for the proposed maximum human dose of 200 mcg/day. Therefore, this finding does not pose a significant human risk.

Chronic inhalation studies were conducted in rats (6 months) and dogs (9 months) in support of the oral inhalation program. Typical systemic glucocorticoid effects (decreases of body eights, adrenal suppression and lymphoid tissue atrophy in thymus, spleen, lymph nodes and bronchus associated lymphoid tissue) were also observed.

Reproductive toxicity: Ciclesonide did not impair fertility in rats. It was not teratogenic or embyrocidal in rats but it was in rabbits. Thus, the drug should be categorized as a pregnancy category C, similar to other corticosteroids.

Genotoxicity: Ciclesonide was not mutagenic in an Ames test and an HGPRT forward mutation assay and was not clastogenic in a human lymphocyte assay and an in vitro micronucleus test in V79 cells. It was, however, clastogenic in an in vivo mouse micronucleus test.

Carcinogenicity: In two 2-year inhalation carcinogencity studies in mice and rats, ciclesonide did not induce any tumors.

Labeling: The proposed nonclinical sections “Clinical Pharmacology”, “Carcinogenesis, mutagenesis and impairment of fertility”, “Pregnancy” and “Nursing mothers” sections were identical to that approved for NDA 22-004 and reviewed by Dr. Huiqing Hao with the exception of a minor edit in the “Pregnancy” section. Dr. Hao recommended that the sponsor include exposure ratio comparisons for animals and humans in the “Carcinogenesis, mutagenesis and impairment of fertility” section to include children aged 6-11 and the sponsor accepted this modification. Otherwise, the relevant sections of the product label appear to be acceptable.

All issues raised during the drug development program regarding ciclesonide-related toxicities observed in the chronic inhalation studies and intranasal bridging studies have

been resolved. Therefore, there are no outstanding preclinical issues. This application is considered approvable from a nonclinical perspective. It is noted that adequate efficacy data has been provided to support only ages 6 and above.

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/s/

Timothy McGovern
10/30/2007 12:15:15 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-124**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**5/24/2007**
PRODUCT:	**OMNARIS (Ciclesonide) Nasal Spray, 50 mcg**
INTENDED CLINICAL POPULATION:	**Allergic Rhinitis in Children (b) (4) 11 Years Old**
SPONSOR:	**Altana Pharma US, Inc.**
DOCUMENTS REVIEWED:	**E-submission, Module 4**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Huiqing Hao, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy McGovern, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Colette Jackson**

Date of review submission to Division File System (DFS): October 29, 2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This drug is recommended to be approved from a pharmacology and toxicology perspective. It is noted that the clinical data support only ages down to 6 years of age at a maximum dose of 200 mcg/day.

B. Recommendation for nonclinical studies
There are no nonclinical studies recommended in view of this NDA submission.

C. Recommendations on labeling
Modified language is recommended for the information pertaining to the section "Carcinogenesis, mutagenesis and fertility". See the "Overall Conclusions and Recommendations" section for recommended revisions to the nonclinical sections of the product label.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No new nonclinical studies other than a kinetic study in pregnant rats were conducted for this NDA submission since OMNARIS Nasal Spray was previously approved (October 2006) for the treatment of seasonal and perennial allergic rhinitis in ages 12 years and older under NDA 22-004. Under that program, the sponsor conducted an abbreviated toxicology program using intranasal administration consisting of 14 and 28-day studies in rats and dogs and a 6-month dog study based on an agreement between the Division and the sponsor regarding a bridging toxicology program to the completed inhalation toxicology program conducted under IND 53,391 and NDA 21-658. Altana obtained right of reference to the inhalation data generated by Aventis.

The intranasal studies identified no local (intranasal) toxicities in rats (up to 429 mcg/kg or 7.7 mcg/cm^2 nasal surface area, 4 weeks). In dogs, nasal associated lymphoid tissue atrophy was observed at the intranasal dose of 4800 mcg/day (21.8 mcg/cm^2 nasal surface area) for 4 weeks and 6 months. The NOAELs for the dog studies were 1200 mcg/day (5.5 mcg/cm^2 nasal surface area). On a mcg/cm^2 nasal surface area basis, the NOAELs in the rat and dog studies provided 6.2- and 4.3-fold safety margins, respectively, regarding local toxicities for the proposed human dose of 200 mcg/day (1.25 mcg/cm^2).

Systemic toxicities observed in the intranasal program are mostly typical for glucocorticoids that have been reported in the inhalation program. Those toxicities include a decrease of body weight (or body weight gain), increase of blood triglyceride and cholesterol levels, adrenal suppression and lymphoid tissue atrophy (thymus, spleen, lymph nodes and bronchus-associated lymphoid tissues). These typical glycocorticoid effects are not considered safety concerns because of the existing clinical experience and/or the presence of sufficient safety margins. In addition to the typical glucocorticoid effects, testicular atrophy was observed in dogs receiving intranasal administration at a high dose of 4800 mcg/day for 6 months. The systemic exposure at the NOAEL dose in this study (1200 mcg/dog/day) correlated with Cmax values of 334 and 295 pg/mL for ciclesnodie and des-ciclesonide, respectively; AUC0-24h of 586 and 1284 pg.h/mL for ciclesonide and des-ceclesonide, respectively. Human serum levels were undetectable following 800 mcg/day intranasal administration in adults or pediatric subjects (lower quantitative limits of 25 pg/mL for ciclesonide and 10 pg/mL for des-ciclesonide). On a mcg/kg basis, the dog NOAEL of 1200 mcg/dog provides a 30-fold safety margin for the proposed maximum human dose of 200 mcg/day. Therefore, this finding does not pose a significant human risk.

Ciclesonide was negative in an Ames test, a CHO/HGPRT forward mutation assay, a chromosome aberration assay in human lymphocytes, and an in vitro micronucleus test in V79 cells. However, ciclesonide was positive in an in vivo micronucleus test in mice.

Two-year carcinogenicity studies in mice (oral dose up to 900 mcg/kg) and rats (inhalation dose up to 193 mcg/kg) demonstrated that this drug did not induce any increase in tumor incidence.

In rat reproductive toxicity studies, ciclesonide showed no toxicities to fertility and early embryo-fetal development, embryo-fetal development or prenatal and postnatal development in rats at oral doses up to 900 mcg/kg. However, in a rabbit study, ciclesonide was found to be teratogenic (subcutaneous, 5 mcg/kg and above) and embryocidal (subcutaneous, 100 mcg/kg). The NOAEL for the teratogenic effects was 1 mcg/kg which is one quarter of the proposed human dose of 4 mcg/kg (200 mcg/day) on a mcg/kg basis. OMNARIS is classified as a Pregnancy Category C drug.

B. Pharmacologic activity

Ciclesonide is a pro-drug as shown by a 120-fold higher binding affinity of its de-esterified metabolite to glucocorticoid receptors. Ciclesonide exhibited immunosuppressive properties: inhibiting lymphocyte proliferation and release of cytokines (IL-2, IL-4, IL-5, TNFα and INF-γ) from lymphocytes and monocytes; inhibiting IL-1β induced IL-8 release in human nasal epithelial cells and bronchial epithelial cells. In a guinea pig allergic rhinitis model, administration of ciclesonide prevented increase of nasal respiratory resistance and increase of eosinophils in nasal lavage fluid.

Compared with the marketed steroid drug fluticasone, ciclesonide appears to be less potent in both anti-inflammatory and typical steroid side effects as studied in lung inflammation models.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues relevant to the proposed clinical use of this product

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

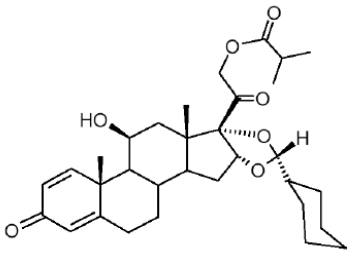
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-124
Review number: 1
Sequence number/date/type of submission: 000/May 24, 2007/AZ
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Altana Pharma US, Inc.
Manufacturer for drug substance: Pfizer Inc.

Reviewer name: Huiqing Hao, Ph.D.
Division name: Pulmonary and Allergy Products
Review completion date: 10/10/2007

Drug:

Trade name: OMMARIS Nasal Spray, 50 mcg
Generic name: Ciclesonide nasal spray
Code name: BYK20426, B9207-015 (drug substance); TBN-15 (drug product)
Chemical name: Pregna-1,4-diene-3,20-dione, 16, 17-{[R-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11b, 16a)-
CAS registry number: 141845-82-1
Molecular formula/molecular weight: $C_{32}H_{44}O_7$, 540.7
Structure:



Relevant INDs/NDAs/DMFs: IND 65,488 (intranasal), IND 53,391 (inhalation) and NDA 22-004 (nasal administration, 12 yrs and older); NDA 21-658 (oral inhalation); DMF of (b) (4) (ciclesonide, micronized), DMFs: (b) (4)

Drug class: Glucocorticoid steroid

Intended clinical population: The proposed clinical indication is for nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children (b) (4) years of age and older. The proposed dose for approval is 200 mcg/day (2 sprays of 50 µg in each

nostril once daily) for ages 6 years and older. (b) (4)

Clinical formulation:

TABLE 3.2.P.1-1: Drug Product Unit Composition

Ingredient	Amount					Function
	mg/actuation[1]	mg/mL	wt %[2]	mg/bottle[3] (b) (4)	120 puff presentation	
Drug Substance:						
Ciclesonide, micronized	0.050	(b) (4)				Active ingredient
Excipients:						
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (b) (4)	(b) (4)					
Potassium Sorbate NF						
Edetate Disodium USP						
Hydrochloric Acid NF q.s. ad						
Purified Water USP q.s. ad						
(b) (4)						

1 Based on a nominal spray volume of (b) (4) per actuation.
2 The conversion from weight to volume was performed using an experimentally determined specific gravity of (b) (4)
3 The stated values are based on a target fill of (b) (4) 120 puff presentations, respectively.
4 (b) (4)

Route of administration: Intranasal administration

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:
Pharmacokinetics of ciclesonide in pregnant rats following repeated oral dosing of ciclesonide (Report No. 370/2005)

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

No new studies were submitted to this NDA. Based on data submitted to NDA 22-004, Ciclesonide is a pro-drug as shown by a 120-fold higher binding affinity of its de-esterified metabolite to glucocorticoid receptor. This drug was shown to have

pharmcodynamic activity relevant to allergic rhinitis. *In vitro* studies showed that ciclesonide inhibited lymphocyte proliferation and cytokine release from lymphocytes and monocytes, and inhibited IL-1β induced IL-8 release from human nasal epithelial cells. In a guinea pig allergic rhinitis model, ciclesonide inhibited the ovalbumin-induced increase in nasal respiratory resistance and the increase of eosinophils in nasal lavage fluid.

Compared with the marketed steroid drug fluticasone, ciclesonide appeared to be less potent in both anti-inflammatory and typical steroid side effects in rat lung inflammation models.

Safety pharmacology studies for ciclesonide revealed no neurological, cardiovascular or respiratory effects. Additionally, ciclesonide and its metabolites had no affinity for estrogen receptors and had very low affinity for progesterone and testosterone receptors.

2.6.2.2 Primary pharmacodynamics
No new studies were submitted.

2.6.2.3 Secondary pharmacodynamics
No new studies were submitted.

2.6.2.4 Safety pharmacology
No new studies were submitted.

2.6.2.5 Pharmacodynamic drug interactions
No new studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

NA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary
No new studies were submitted to this NDA other than a kinetic study in pregnant rats. Based on data submitted to IND 53,391, and NDAs 22-004 and 21-658, oral bioavailability is less than 6% in most species due to an extensive first pass effect. Both ciclesonide and RM-1 have a large volume of distribution (4-6 L/kg in rats, mice and dogs). The T1/2 of ciclesonide was short (1 hour in rats and mice) which is probably due to conversion of ciclesonide to RM-1. T1/2 of RM-1 was 2.4 to 7 hours in rats, mice, rabbits, and dogs. Absorbed ciclesonide was distributed widely and organs with high concentration of ciclesonide and/or RM-1 were lung, heart, thyroid, adrenals, liver, and kidneys. Following repeated oral administration of ciclesonide to pregnant rats, systemic exposure was confirmed based on serum concentrations of the active metabolite M1 (B9207-021). On day 21 p.c., concentrations of B9207-021 in the serum of fetuses were

less than 0.13% compared to that of the dams at a dose of 0.9 mg/kg, indicating a low penetration of the placenta by ciclesonide and/or the M1 metabolite.

Systemically absorbed ciclesonide is rapidly de-esterified to active metabolite RM-1 and RM-1 is further metabolized to several products. 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 T1/2 = 1-2 hours in nasal mucosa homogenates from rats, rabbits, guinea pigs and dogs).

The major systemic elimination pathway is bile and feces (80%). The elimination rates in animals were equal or greater than hepatic blood flow rate. Exposure to ciclesonide and/or RM-1 does not induce or inhibit liver enzymes.

Both ciclesonide and RM-1 were approximately 99% plasma protein bound in all species studied.
Toxicokinetic data were not obtained in rat intranasal studies (14-Day and 28-Day, doses up to 480 ug/kg) due to low plasma levels (below QL of 0.25 ng/mL). Three dog intranasal studies (14-Day, 28-Day and 26-Week up to approximately 480 ug/kg) revealed similar TK profiles: dose proportional drug exposures (Cmax and AUC), no drug accumulation over 26 weeks and no gender related differences noted.

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

No new studies were submitted.

2.6.4.4 Distribution

Study title: Pharmacokinetics of ciclesonide in pregnant rats following repeated oral dosing of ciclesonide (Report No. 370/2005)

This is a GLP study conducted by Altana and the study initiation date was 6/30/2003.

In this study, 20 female Wistar rats were given an oral (gavage) dose of 0.9 mg/kg/day in PEG400 of ciclesonide during Days 6-21 post coitum (p.c.). Serum concentrations of B9207-021 (ciclesonide metabolite M1) were measured (at 0.5, 1, 2, 6, 8 and 24 h post dose) on Days 13, 14 or 15 p.c. in pregnant rats and on Day 21 in dams and fetuses at 0.5 hour following the last dose.

The drug was isolated from rat serum after quantitative conversion of present ciclesonide into B9707-021 by incubation with esterases followed by solid phase extraction and

HPLC-MS/MS analysis. Lower limit of quantitation (LLOQ) was 62.5 pg/mL for 200 mcL.

B9207-021 was observed in the serum of pregnant rats; PK parameter estimates of B9207-021 in pregnant rats following repeated oral administration of 0.9 mg/kg/day on Days 13, 14 or 15 p.c. are the following (geometric mean values):

	0.9 mg/kg p.o. ciclesonide
PK parameter	B9207-021
$AUC_{(0, 8h)}$ (µg·h/L)	14.31
C_{max} (µg/L)	11.96
t_{max} (h)	0.5
$t_{1/2}$ (h)	not ascertained

$AUC_{(0, 8h)}$ area under the serum concentration versus time curve from time zero to time 8 h
C_{max} maximum concentration t_{max} maximum time
$t_{1/2}$ terminal elimination half-life

The median serum concentration of pregnant rats on Day 13, 14 or 15 of gestation following repeated oral dosing was 14.6 mcg/L at 0.5 hour post dosing.

On Day 21 p.c., 0.5 h post dosing, the median serum concentration of B9207-021 was 50.01 mcg/L which is ~ 3-fold higher than the corresponding serum concentrations (14.6 mcg/L) on Day 13, 14 or 15 p.c. Low levels of B9207-021 were observed in the fetuses; serum concentrations of B9207-021 in fetuses were between LLOQ (0.0625 mcg/L) and 0.1956 mcg/L (median value < 0.0625 mcg/L) following the last dose of 0.9 mg/kg ciclesonide on Day 21 p.c. to the dams. Thus, fetal serum concentrations were < 0.13% of the maternal serum concentrations.

In conclusion, following repeated oral administration of ciclesonide, systemic exposure in pregnant rats was confirmed based on serum concentrations of the active metabolite M1 (B9207-021). On day 21 p.c., concentrations of B9207-021 in the serum of fetuses were less than 0.13% compared to that of the dams at a dose of 0.9 mg/kg, indicating a low penetration of the placenta by ciclesonide and/or metabolite.

2.6.4.5 Metabolism
No new studies were submitted.

2.6.4.6 Excretion
No new studies were submitted.

2.6.4.7 Pharmacokinetic drug interactions
No new studies were submitted.

2.6.4.8 Other Pharmacokinetic Studies
No new studies were submitted.

2.6.4.9 Discussion and Conclusions

Most pharmacokinetic data were submitted and reviewed under NDAs 21-658 and 22-004. Ciclesonide has a low oral bioavailability (<6%) in animals and humans. Systemically absorbed ciclesonide is rapidly de-esterified to the active metabolite RM-1 and RM-1 is further metabolized to several products. 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. The plasma T1/2 of ciclesonide was short (1 hour in rats and mice) which is probably due to conversion of ciclesonide to RM-1. T1/2 of RM-1 was 2.4 to 7 hours in rats, mice, rabbits, and dogs.

Systemically absorbed ciclesonide was distributed widely and the organs with high concentration of ciclesonide and/or RM-1 were lung, heart, thyroid, adrenals, liver, and kidneys. A kinetic study in pregnant rats demonstrated a low penetration of the placenta by ciclesonide and/or the M1 metabolite. Both ciclesonide and RM-1 were approximately 99% plasma protein bound in all species studied. The major elimination pathway is bile and feces (80%). The elimination rates in animals were equal or greater than hepatic blood flow rate. Exposure to ciclesonide and/or RM-1 does not induce or inhibit liver enzymes.

Three dog intranasal studies revealed similar TK profiles: dose proportional drug exposures (Cmax and AUC), no drug accumulation over 26 weeks and no gender related differences noted. Rat data were not available.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

NA

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

The sponsor has obtained authorization from Aventis Pharmaceuticals to reference IND 53,391 and NDA 21-658 (Alvesco, ciclesonide metered dose inhaler). Based on the systemic toxicity data obtained in the inhalation program conducted by Aventis for for treatment of asthma, the Division agreed that a bridging toxicology program consisting of up to a 6 month intranasal toxicology study in an appropriate species would satisfy the preclinical requirements for the current NDA and NDA 22-004. Therefore, the toxicity data were mostly obtained through the inhalation program. The intranasal bridging program was to study local and systemic toxicities following the intranasal administration.

The minimum lethal doses of ciclesonide in mice and rats were 200 mg/kg by

intraperitoneal administration and the maximum non-lethal doses were 100 mg/kg in these studies. In rat and mouse oral studies, the minimum lethal doses were not defined and the maximum non-lethal doses were 2000 mg/kg in both rats and mice.

Under NDA 21-658, repeat dose toxicity studies including rat studies of 4 weeks and 6 months each with inhalation, oral and subcutaneous administration route, and dog studies using administration routes of inhalation (4 weeks, 3 months, 6 months and 12 months), oral administration (4 weeks and 12 months) and intravenous infusion (2 weeks) were reviewed. Major toxicities observed in theses studies were typical for glucocorticoids including decreased body weights, slight increases in blood triglyceride and cholesterol levels, adrenal suppression, and lymphoid tissue atrophy. Additionally, skin hair follicle regression, ovarian atrophy and thickened lung alveolar septa were seen in the 12-month dog inhalation study. The details of these studies and identified NOAELs can be found in the review for NDA 21-658.

Toxicity studies with intranasal route of administration were submitted under IND 65,488. The completed intranasal studies include studies of 14 and 28 days in rats, 14 and 28 days and 6 months in dogs.

Rat studies showed no local toxicity in the presence of systemic toxicities of typical glucocorticoid effects. Testicular atrophy was initially identified in a rat 4-week intranasal study but was concluded to be not treatment related due to the lack of similar finding at higher systemic exposures with similar or longer treatment durations.

The dog intranasal studies revealed both local and systemic toxicities. The local toxicities were lymphoid aggregates in nasal mucosa (in the 28-day study) and nasal lymphoid atrophy (in the 6-month study). Systemic toxicities in the 14- and 28-day dog studies were body weight decrease, adrenal suppression, lymphoid atrophy and blood chemistry changes. In addition to these typical steroid effects, 6-month dog intranasal study showed increase of incidence/severity of seminiferous tubular atrophy, vacuolation and mononuclear cell infiltrations at the high dose of 4800 ug/body (corresponding $AUC_{0\text{-}24\ h}$ of 1161 pg.h/mL of RM-1 and 552 pg.h/mL of ciclesonide). The testicular finding in the 6-month dog intranasal study was not reported in the previous inhalation studies for up to 12 months with 50-60 fold lower AUC levels. Therefore, the testicular toxicity finding in the intranasal study probably reflects the effect of the high dose. This toxicity is not relevant to humans because intranasal use of ciclesonide up to the maximum recommended dose of 200 ug/day produces negligible levels of systemic drug exposure. Based on the relative dose comparisons between animals and humans, the animal studies provide sufficient safety margins for the observed local toxicities at the maximum proposed human dose of 200 ug/day based on nasal surface area comparisons (see the table below).

Species	Dosing duration	Dose (ug/kg)	NOAEL (ug/kg)	NOAEL dose converted to μg/cm^2	Safety margin[b]	Report No
Rat	14 days	107, 429	429	7.7	6.2	218/2001
Rat	28 days	107, 214, 429	429	7.7	6.2	22/2001
Dog	14 days	120, 480	480	21.7	17.4	219/2001
Dog	28 days	120, 240, 480	120	5.43	4.3	16/2002
Dog	6 months	300[a], 1200[a], 4800[a]	1200[a]	5.43	4.3	103/2004
Human[c]	-	200 μg	-	1.25	-	-

[a]. ug/dog; [b]. safety margins for the maximum recommended human dose of 200 ug/day based on nasal exposure assuming mucosal surface area of 160, 221 and 14 cm^2 in humans, dogs, and rats, respectively, and assuming body weights of 250 g for rats and 10 kg for dogs; [c]. Proposed maximum clinical dose

In conclusion, the intranasal bridging toxicity program identified no additional systemic toxicities in comparison to studies with other routes of administration and provided appropriate margins of safety for the proposed intranasal use of ciclesonide.

Genetic toxicology: Studies regarding the genotoxic potential of ciclesonide were reviewed under IND 53,391 (review of the original submission). Ciclesonide was negative in Ames test, chromosome aberration assay in human peripheral lymphocyte, CHO/HGPRT forward mutation assay, and in vitro micronucleus test in V79 cells, but was positive in the in vivo mouse micronucleus test.

Carcinogenicity: Studies regarding the carcinogenic potential of ciclesonide were reviewed under IND 53,391 (review #12 for the submission dated 08/15/2002). Two-year carcinogenicity studies were conducted in mice by oral gavage at doses of 150, 450 and 900 μg/kg and in rats by inhalation at delivered doses of 30, 76 and 193 μg/kg. Ciclesonide did not increase any tumor incidences in mice and rats.

Reproductive toxicology: Studies regarding the reproductive toxicity of ciclesonide were reviewed under IND 53,391 (original review and review #7 for the submission dated 02/19/1999) and NDA 21-658.

Ciclesonide does not affect fertility, embryo-fetal development or prenatal and postnatal development in rats as tested by oral administration at doses up to 0.9 mg/kg/day. However, ciclesonide is teratogenic in rabbits. In rabbits, subcutaneous treatment with ciclesonide (25, 100, and 400 μg/kg) resulted in post-implantation loss and reduced litter weight at doses of 100 μg/kg and above. There were no living fetuses in the 400 μg/kg dose group. Fetal weights were reduced at doses of 25 μg/kg and above. Treatment related skeletal and visceral changes in the fetuses included cleft palates, acampsia,

largeness of fontanelle, pergameneous skin, microtia, exencephaly, ablepharia, umbilical hernia, dysmelia, cranial meningocele, exencephaly, beachdactyly. Thus, this drug was teratogenic at doses of 25 μg/kg and above and embryocidal at 100 μg/kg and above. A study with lower subcutaneous doses (1, 5 and 25 μg/kg) in rabbits demonstrated fetal toxicities including slight decrease of fetal body weights, flexure of legs, and cleft palate, but no maternal toxicities. The dose of 1 μg/kg was defined as the NOAEL based on the findings of flexure of legs in the next higher dose level.

Special toxicology: It was reported (IND 53,391, review #8 for the submission dated 03/13/2000) that Ciclesonide was negative in anaphylaxis reaction as tested in active systemic anaphylaxis and passive cutaneous anaphylaxis in guinea pigs and in mice-rats passive cutaneous anaphylaxis test.

Local tolerance study: The clinical formulation with strengths of 25 ug/actuation and 100 ug/actuation showed no irritation to rabbit eyes. Additionally, a non-GLP 28-day rabbit nasal tolerance study was conducted to assess a hypotonic formulation that did not include ciclesonide. The hypotonic formulation showed no irritation effects to the nasal mucosa.

2.6.6.2 Single-dose toxicity
No new studies were submitted.

2.6.6.3 Repeat-dose toxicity
No new studies were submitted.

2.6.6.4 Genetic toxicology
No new studies were submitted.

2.6.6.6 Reproductive and developmental toxicology
No new studies were submitted.

2.6.6.7 Local tolerance
No new studies were submitted.

2.6.6.8 Special toxicology studies
No new studies were submitted.

2.6.6.9 Discussion and Conclusions
The toxicities of ciclesonide as a result of systemic exposure have been reported and reviewed under IND 53,391 and NDA 21-658 for the inhalation use of ciclesonide. The primary nonclinical concern for the current NDA and NDA 22-004 is the potential for local effects following intranasal administration. In this regard, it was agreed that the sponsor should conduct an abbreviated toxicology program to bridge the available

nonclinical data by other routes of administration to address the toxicities of the proposed intranasal route of administration. This bridging program consisted of studies up to a 6-month intranasal study in an appropriate species based on the results of shorter term studies in two species. Under IND 65,488 or in NDA 22-004, intranasal toxicology studies in rats (14-day and 28-day) and dogs (14-day, 28-day and 6-month) were reported.

The intranasal studies identified no local (intranasal) toxicities in rats (up to 429 mcg/kg or 7.7 mcg/cm^2 nasal surface area, 4 weeks). In dogs, nasal associated lymphoid tissue atrophy was observed at the intranasal dose of 4800 mcg/day (21.8 mcg/cm^2 nasal surface area) for 4 weeks and 6 months. The NOAELs for the dog studies were 1200 mcg/day (5.5 mcg/cm^2 nasal surface area). On a mcg/cm^2 basis, the dog study provided 4.3-fold safety margin, regarding local toxicities for the proposed human dose of 200 mcg/day (1.25 mcg/cm^2).

Systemic toxicities observed in the intranasal program are mostly typical for glucocorticoids that have been reported in the inhalation program. Those toxicities include a decrease of body weight (or body weight gain), increased blood triglyceride and cholesterol levels, adrenal suppression and lymphoid tissue atrophy (thymus, spleen, lymph nodes and bronchus-associated lymphoid tissues). These typical glycocorticoid effects are not significant safety concerns because of the existing clinical experience and/or sufficient safety margins. In addition to the typical glucocorticoid effects, testicular atrophy was observed in dogs receiving intranasal administration at a high dose of 4800 mcg/day for 6 months. The systemic exposure at the NOAEL dose in this study (1200 mcg/dog/day) correlated with Cmax values of 334 and 295 pg/mL for ciclesonide and des-ciclesonide, respectively; AUC0-24h of 586 and 1284 pg.h/mL for ciclesonide and des-ciclesonide, respectively. Human serum levels were undetectable following 800 mcg/day intranasal administration in adults or pediatric subjects (lower quantitative limits of 25 pg/mL for ciclesonide and 10 pg/mL for des-ciclesonide). On a mcg/kg basis, the dog NOAEL of 1200 mcg/dog provides a 30-fold safety margin for the proposed maximum human dose of 200 mcg/day. Therefore, this finding does not pose a significant human risk.

The bridging toxicology program conducted by the sponsor for the proposed intranasal use of ciclesonide identified no new systemic target organs of toxicity that are clinically relevant and appropriate safety margins are available for the identified local effects. Therefore, there is no nonclinical safety concern for the proposed human intranasal use of ciclesonide up to 200 mcg/day.

Local tolerance studies demonstrated a lack of an irritant effect of a hypoosmotic solution in the nasal cavity and of the proposed formulation on the eye.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
NDA 22-004, OMNARIS (ciclesonide) Nasal Spray was submitted on 12/22/2005 for treatment of seasonal and perennial allergic rhinitis in patients aged (b) (4) years and old. (b) (4)

NDA 22-124 for patients (b) (4) 11 years age and NDA 22-004 for patients 12 years and older (see CSO's memo on 10/18/2006). An Approvable letter for NDA 22-124 was sent to the sponsor on October 20, 2006 (b) (4)

No new nonclinical data with the exception of a kinetic study in pregnant rats were submitted to this NDA (b) (4) . The kinetic study in rats does not affect this conclusion.

The current NDA (22-124) pursues use of OMNARIS in children (b) (4) 11 years of age. However, the proposed labeling information includes that for adults and children. (b) (4) A slight modification in the labeling regarding animal to human exposure ratios is recommended to include relevant exposure ratios in children aged 6-11 (see the suggested labeling below).

As stated above, the only nonclinical data submitted under this NDA is an oral PK study in rats. The study demonstrated that 0.13% of maternal plasma drug penetrated placenta and reached fetal blood. However, this result does not warrant any further revision of the product labeling.

Unresolved toxicology issues (if any): None

Recommendations: This NDA is recommended for approval provided with suggested labeling revisions.

Suggested labeling:
The sponsor submitted proposed product labeling in the submission dated 5/24/2007. This labeling is identical to the labeling approved by the Division for NDA 22-004 (for

treatment of patients ages 12 and older) in October 2006. As the indicated population in the current NDA includes children 6-11 years old, the exposure margins expressed in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section should be modified to reflect exposure ratios for the younger age group (see the attachment for the exposure ratio calculation).

The remaining nonclinical sections of the product label are acceptable. Of note, the sponsor edited the second paragraph of the "Pregnancy" section from "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 in humans." to "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." This change is acceptable.

Recommendations for labeling revision are provided below (underlines for additions):

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 and 10 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m^2) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 and 5 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m^2) in rats 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 35 times the maximum human daily intranasal dose in adults based on mcg/m^2).

Signatures (optional):

Reviewer Signature _Huiqing Hao, Ph.D._____

Supervisor Signature__Timothy McGovern, Ph.D._____ Concurrence Yes ___ No ___

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/s/

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10/29/2007 01:55:44 PM
PHARMACOLOGIST

Timothy McGovern
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I concur.