

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-004**

**PHARMACOLOGY REVIEW**

**MEMORANDUM**

Oct. 20, 2006

TO: File

FROM: Kenneth L. Hastings, Dr.P.H., D.A.B.T.

SUBJECT: NDA 22-004

I concur with Drs. Huiqing Hao and Timothy McGovern that the marketing application for Ciclesonide nasal spray may be approved based on review of submitted pharmacology/toxicology data.

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Kenneth L. Hastings, Dr.P.H., D.A.B.T.  
Associate Director  
Office of New Drugs

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/s/

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Kenneth Hastings  
10/20/2006 01:31:34 PM  
PHARMACOLOGIST

## Supervisory Pharmacologist Review

**NDA:** 22-004 - Ciclesonide Nasal Spray  
**FROM:** Timothy J. McGovern, Ph. D., Supervisory Pharmacologist  
**DATE:** September 8, 2006

I concur with the recommendation by Dr. Huiqing Hao, the pharmacology/toxicology reviewer, that the pharmacology and toxicology of ciclesonide nasal spray have been adequately studied and evaluated and that the drug product is approvable from a nonclinical standpoint (see review dated August 30, 2006). In regard to the nonclinical data, the application referenced much of the data generated for [REDACTED] ciclesonide inhalation solution, which is also considered to be approvable at this time. For the current application, 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-1 $\beta$ -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 conducted a complete program for the inhalation route of administration under [REDACTED]. The sponsor 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> nasal surface area). On a mcg/cm<sup>2</sup> 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<sup>2</sup>).

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 C<sub>max</sub> values of 334 and 295 pg/mL for ciclesonide and des-ciclesonide, respectively; AUC<sub>0-24h</sub> 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 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.

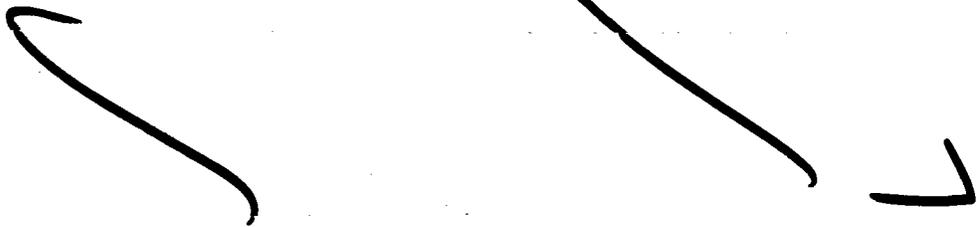
Chronic inhalation studies were conducted in rats (6 months) and dogs (9 months) in support of the oral inhalation program. Typical systemic glucocorticoid effects (decreases of body weights, adrenal suppression and lymphoid tissue atrophy in thymus, spleen, lymph nodes and bronchus associated lymphoid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

Reproductive toxicity: Ciclesonide did not impair fertility in rats. It was not teratogenic or embryocidal 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 carcinogenicity studies in mice and rats, ciclesonide did not induce any tumors.

Labeling: **E**



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.

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/s/

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Timothy McGovern  
9/8/2006 08:11:33 AM  
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: 22-004  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 12/21/05  
PRODUCT: Ciclesonide nasal spray  
INTENDED CLINICAL POPULATION: Adults and children 2 years of age and older with seasonal and perennial allergic rhinitis  
SPONSOR: Altana Pharm US, Inc  
DOCUMENTS REVIEWED: Electronic NDA, 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: Collette Jackson

Date of review submission to Division File System (DFS): August 30, 2006

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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.

#### **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 mechanism of action, carcinogenesis, impairment of fertility, pregnancy, nursing mother, and over dosage. See "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**

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 with the sponsor regarding a bridging toxicology program to the completed inhalation toxicology program.

The intranasal studies identified no local (intranasal) toxicities in rats (up to 429 mcg/kg or 7.7 mcg/cm<sup>2</sup> 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<sup>2</sup> nasal surface area) for 4 weeks and 6 months. The NOAELs for the dog studies were 1200 mcg/day (5.5 mcg/cm<sup>2</sup> nasal surface area). On a mcg/cm<sup>2</sup> 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<sup>2</sup>).

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 glucocorticoid 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 C<sub>max</sub> values of 334 and 295 pg/mL for ciclesnoidic and des-ciclesonide, respectively; AUC<sub>0-24h</sub> 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 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 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.

#### 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, TNF $\alpha$  and INF- $\gamma$ ) from lymphocytes and monocytes; inhibiting IL-1 $\beta$  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:** 22-004

**Review number:** 1

**Sequence number/date/type of submission:** 000/Dec.21, 2005/original; 009/May 4, 2006/SU

**Information to sponsor:** Yes (X) No ( )

**Sponsor and/or agent:** Altana Pharm US, Inc.

**Manufacturer for drug substance:** ~~XXXXXXXXXX~~

**Reviewer name:** Huiqing Hao

**Division name:** Pulmonary and Allergy Products

**Review completion date:** 8/30/06

**Drug:**

Trade name: Not available

Generic name: Ciclesonide nasal spray

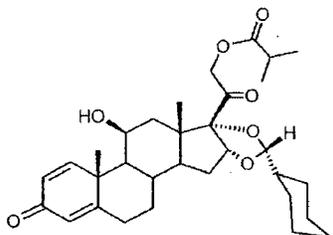
Code name: BYK20426, B9207-015 (drug substance); TBN-15 (drug product)

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<sub>32</sub>H<sub>44</sub>O<sub>7</sub>, 540.7

Structure:



**Relevant INDs/NDAs/DMFs:** IND 65,488 (intranasal), ~~XXXXXXXXXX~~

**Drug class:** Glucocorticoid steroid

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

The proposed doses produce negligible systemic exposure (serum concentrations below the quantitative limits of 25 pg/mL and 10 pg/mL for ciclesonide and des-ciclesonide, respectively) in humans.

Note: Currently, the clinical review team considers that the efficacy data for this drug product does not support approval for use of patients aged 12 years old or younger.

**Clinical formulation:**

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

| Ingredient                                                      | Amount                    |       |                   |                        | Function          |
|-----------------------------------------------------------------|---------------------------|-------|-------------------|------------------------|-------------------|
|                                                                 | mg/actuation <sup>1</sup> | mg/mL | wt % <sup>2</sup> | mg/bottle <sup>3</sup> |                   |
|                                                                 |                           |       |                   | 120 puff presentation  |                   |
| <b>Drug Substance:</b>                                          |                           |       |                   |                        |                   |
| Ciclesonide                                                     | 0.050                     |       |                   |                        | Active ingredient |
| <b>Excipients:</b>                                              |                           |       |                   |                        |                   |
| Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF |                           |       |                   |                        |                   |
| Potassium Sorbate NF                                            |                           |       |                   |                        |                   |
| Edetate Disodium USP                                            |                           |       |                   |                        |                   |
| Hydrochloric Acid NF                                            | q.s. ad                   |       |                   |                        |                   |
| Purified Water USP                                              | q.s. ad                   |       |                   |                        |                   |

**Route of administration:** Intranasal administration

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

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-004 are owned by Altana or are data for which Altana has obtained a written right of reference. Any information or data necessary for approval of NDA 22-004 that Altana does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Altana does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-004.

**Studies reviewed within this submission:**

|                                                                                                                                                                                                                                                    | Study No |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <b>Pharmacodynamics</b>                                                                                                                                                                                                                            |          |
| In vitro effects of ciclesonide on glucocorticoid signaling pathway in the human lung, comparison with dexamethasone, budesonide, and fluticasone.                                                                                                 | 69/2005  |
| Ciclesonide: in-vivo pharmacology evaluation                                                                                                                                                                                                       | 28/2001  |
| Effects of ciclesonide and fluticasone propionate on allergen-induced chronic airway inflammation and bronchial hyperresponsiveness in sensitized brown-norway rats                                                                                | 160/2003 |
| <b>Toxicity</b>                                                                                                                                                                                                                                    |          |
| Ciclesonide nasal spray: 28 day nasal administration toxicity study in the male rat with a 28 day treatment-free period                                                                                                                            | 49/2003  |
| <b>Local tolerance</b>                                                                                                                                                                                                                             |          |
| 28-day repeated nasal irritation study of hypotonic suspension preparation in rabbits                                                                                                                                                              | 303E/99  |
| Primary eye irritation study of ciclesonide nasal spray in rabbits                                                                                                                                                                                 | 344/2003 |
| <b>metabolism</b>                                                                                                                                                                                                                                  |          |
| Determination of the concentration of ciclesonide (B9207-015) and its metabolite (B9207-021, M1) in nasal mucosal tissues after intranasal administration of ciclesonide suspension to rabbits – Comparison of hypotonic and isotonic formulations | 239/2002 |
| In vitro metabolism of ciclesonide in various animal nasal mucosal homogenates from rats, guinea pigs, rabbits and dogs                                                                                                                            | 45/2003  |

**Studies not reviewed within this submission (have been reviewed previously)**

| Study Title                                                                                                                           | Study No | Review location |
|---------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|
| <b>Pharmacology</b>                                                                                                                   |          |                 |
| Binding affinities of ciclesonide analogs to the glucocorticoid receptor of rat lung                                                  | 123E/93  | }               |
| Binding affinities of ciclesonide metabolites M2, M3a and M5 in the glucocorticoid receptor binding assay                             | 266/99   |                 |
| Binding affinities of BYK199393 and BYK204147 (ciclesonide metabolites of the M4 family) in the glucocorticoid receptor binding assay | 237/2001 |                 |
| Binding study of four compounds in estrogen, progesterone and testosterone receptor assays                                            | 45E/96   |                 |
| Characterization of BYK20432 – a report on the action of BYK20432 through the glucocorticoid and progesterone receptors               | 204/2001 |                 |
| Inhibition of ConcanavalinA-stimulated rat spleen cells by ciclesonide, its R- and Sepimer and their metabolites, and by Budesonide   | 89/94    |                 |
| Inhibition of ConA-induced proliferation of human peripheral blood mononuclear cells by B9207-015, B9207-016, B9207-021, B9207-       | 53/95    |                 |

|                                                                                                                                                                                                                  |          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| 022, budesonide and Dexamethasone                                                                                                                                                                                |          |
| Inhibition of CD3-mediated proliferation of human peripheral blood mononuclear cells by BYK20432, BYK20702, BYK54297, BYK55327 and BYK54609                                                                      | 7/99     |
| Inhibition of the IL-2 production of CD3-stimulated human peripheral blood mononuclear cells by B9207-015, B9207-016, B9207-021 and budesonide                                                                   | 90/94    |
| Inhibition of anti-CD3-induced cytokine synthesis in mouse TH2 lymphocytes by ciclesonide (B9207-015) and the ciclesonide metabolite B9207-021                                                                   | 45/94    |
| Inhibition of anti-CD3/CD28 mAb-stimulated human CD4+ T-cell functions by B9207-015                                                                                                                              | 61/2001  |
| Effect of B9207-015 on lipopolysaccharide-induced tumor necrosis factor-alpha release in human whole blood                                                                                                       | 271/2000 |
| Effect of B9207-015 on lipopolysaccharide-induced tumor necrosis factor-alpha release in human monocytes and monocyte-derived dendritic cells                                                                    | 274/2000 |
| Attenuation of bradykinin-induced mucosal leakage in rat trachea by topical ciclesonide                                                                                                                          | 67/95    |
| Attenuation of bradykinin-induced mucosal leakage in rat trachea by topical budesonide                                                                                                                           | 193/94   |
| Study on the effect of ciclesonide in a guinea pig model of allergic rhinitis                                                                                                                                    | 232/2002 |
| <b>Secondary Pharmacodynamics</b>                                                                                                                                                                                |          |
| Effects of single intratracheal powder instillation of ciclesonide on cell accumulation and protein concentration in BAL of ovalbumin-sensitized Brown-Norway rats                                               | 112/96   |
| Effects of single intratracheal administration of B9299-011 on cell accumulation and protein concentration in BAL of ovalbumin-sensitized Brown-Norway rats                                                      | 72/96    |
| Effects of intratracheally administered ciclesonide, its metabolite R-M1 and budesonide on cell and protein accumulation in 48h-bronchoalveolar lavage fluid of ovalbuminsensitized/challenged Brown-Norway rats | 49/2001  |
| Study on the effect of inhaled ciclesonide in a rat model of allergen sensitized and induced airway hyperresponsiveness                                                                                          | 128/2001 |
| Study on the effect of inhaled ciclesonide in a rat model of asthma                                                                                                                                              | 129/2001 |
| Reduction of croton oil-induced mouse ear oedema by R-epimer of ciclesonide and its metabolite B9207-021                                                                                                         | 80/94    |
| Reduction of croton oil-induced mouse ear oedema by budesonide                                                                                                                                                   | 87/94    |
| Comparison of the antiproliferative activity of ciclesonide and its                                                                                                                                              | 202/93K  |

|                                                                                                                                                                                                |          |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|--|
| epimers after local administration in the rat (Cotton pellet granuloma test)                                                                                                                   |          |  |
| Comparison of the antiproliferative activity of the metabolite of ciclesonide (the 'Repimer') and of the metabolite of the S-epimer of ciclesonide in the rat (Cotton pellet granuloma test)   | 123/2001 |  |
| Antiproliferative activity of budesonide after local administration in the rat (Cotton pellet granuloma test)                                                                                  | 77/94    |  |
| Effects on renal function and serum glucose after single intraperitoneal administration of B9207-015 or B9207-016 to rats                                                                      | 37/96    |  |
| Mineralocorticoid and glucocorticoid activity of orally administered ciclesonide, budesonide, metabolite I, epimer R and epimer S in the rat (28 days)                                         | 82E/94   |  |
| <b>Safety Pharmacology</b>                                                                                                                                                                     |          |  |
| Influence of B9207-015 i.v. on behaviour of female rats                                                                                                                                        | 95/04    |  |
| Influence of B9207-015 i.v. on behaviour of female mice                                                                                                                                        | 96/94    |  |
| Influence of intravenous administration of ciclesonide on heart rate, blood pressure and ECG in conscious dogs with concomitant measurement of serum concentrations of B9207-015 and B9207-021 | 194/2001 |  |
| Haemodynamic and respiratory effects of B9207-015, administered as i.v. infusion to anaesthetized cats                                                                                         | 99/94    |  |
| <b>Pharmacokinetics</b>                                                                                                                                                                        |          |  |
| <b>Absorption</b>                                                                                                                                                                              |          |  |
| Pharmacokinetics of metabolite B9207-021 in the female rabbit following a single subcutaneous and intravenous dose of ciclesonide                                                              | 219/2000 |  |
| Pharmacokinetics of [14C]-ciclesonide in the dog following a single intravenous and oral dose                                                                                                  | 93/96    |  |
| Comparison of pharmacokinetics and pharmacodynamics (suppression of cortisol) in dogs following intravenous injection of B9207-021 itself or as prodrug B9207-015                              | 239/98   |  |
| <b>Distribution</b>                                                                                                                                                                            |          |  |
| Tissue distribution of [14C]-ciclesonide in the rat following a single intravenous, oral and intratracheal dose                                                                                | 117/96   |  |
| Whole-body autoradiographic study of [14C]-ciclesonide in the rat following a single intravenous and oral dose                                                                                 | 214/99   |  |
| Placental transfer and mammary glandular passage of [14C]-ciclesonide in the rat                                                                                                               | 172/99   |  |
| <b>Metabolism</b>                                                                                                                                                                              |          |  |
| In vitro metabolism of ciclesonide in the rat lung using precision-cut tissue slices                                                                                                           | 105/2001 |  |
| Investigation of the in vitro formation of the major ciclesonide metabolite I                                                                                                                  | 10/96    |  |
| In vitro metabolism of ciclesonide in the dog using precision-cut liver slices and liver microsomes                                                                                            | 280/99   |  |
| In vitro metabolism of [14C]-ciclesonide by animal and human liver microsomes                                                                                                                  | 71/98    |  |
| <b>Toxicology</b>                                                                                                                                                                              |          |  |
| <b>Single dose</b>                                                                                                                                                                             |          |  |

|                                                                                                                                                                  |           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Single dose toxicity after oral administration of B9207-015 to mice                                                                                              | 94/94     |
| Single dose toxicity after intraperitoneal administration of B9207-015 to mice                                                                                   | 164/94    |
| Single dose toxicity after oral administration of B9207-015 to rats                                                                                              | 106/94    |
| Single dose toxicity after intraperitoneal administration of B9207-015 to rats                                                                                   | 165/94    |
| <b>Repeat dose</b>                                                                                                                                               |           |
| Ciclesonide nasal spray: 14 day nasal administration toxicity study in the rat (screening)                                                                       | 218/2001  |
| Ciclesonide nasal spray: 28 day nasal administration toxicity study in the rat                                                                                   | 221/2001  |
| 28-day inhalation study of B9207-015 in Sprague-Dawley rats                                                                                                      | 121E/94   |
| Toxicokinetics of ciclesonide in a 4-week inhalation toxicity study in Sprague-dawley rats (aerosol generated from powder) + Addendum No. 1 12-Jan-2000          | 197/97    |
| 28-day inhalation toxicity study of B9207-015 in metered dose inhaler (MDI) in wistar (WU) rats                                                                  | 92E/97    |
| Toxicokinetics of ciclesonide in a 4-week inhalation toxicity study in wistar rats (aerosol generated from metered dose inhalers) + Addendum No. 1 (12-Jan-2000) | 199/97    |
| 6-month inhalation study of B9207-015 in Sprague-Dawley rats – Report Amendment (11-Jul-1996 and 14-Nov-1997)                                                    | 138E/95K1 |
| Toxicokinetics of ciclesonide in a 6-month inhalation toxicity study in Sprague-Dawley rats (aerosol generated from powder) + Addendum No. 1 (12-Jan-2000)       | 198/97    |
| The toxicity of B9207-015 after oral administration in the rat for 4 weeks                                                                                       | 76/94     |
| The toxicity of B9207-015 after oral administration in the rat for 6 months                                                                                      | 223/96    |
| Toxicokinetics of ciclesonide in a 6-month oral toxicity study in Wistar rats                                                                                    | 222/97    |
| Ciclesonide nasal spray: 14 day nasal administration toxicity study in the dog (screening)                                                                       | 219/2001  |
| Ciclesonide nasal spray: 28 day nasal administration toxicity study in the dog with a 28 day treatment-free period                                               | 16/2002   |
| A 26-Week Intranasal Toxicity Study of Ciclesonide Nasal Spray in Beagles Followed by a 12-Week Recovery Period                                                  | 103/2004  |
| Toxicity of B9207-015 in beagle dogs following inhalation for 4 weeks                                                                                            | 205/94    |
| Toxicity of B9207-015 in beagle dogs following inhalation from MDI (metered dose inhaler) for 4 weeks                                                            | 103/97    |
| Toxicokinetics of ciclesonide and metabolite B9207-021 in a 4-week low dose inhalation toxicity study in beagle dogs (aerosol generated from a MDI)              | 156/98    |
| Toxicity of ciclesonide in beagle dogs following inhalation as powder aerosol/as MDI generated aerosol for 3 months                                              | 273/98    |
| Toxicokinetics of ciclesonide and metabolite B9207-021 in a 3-                                                                                                   | 19/99     |

|                                                                                                                                                    |           |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| month inhalation toxicity study in beagle dogs (aerosol generated from MDI and powder)                                                             |           |
| Toxicity of ciclesonide R-epimer and ciclesonide S-epimer in beagle dogs as dry powder aerosol inhalation for 3 months                             | 131/2003  |
| Toxicity of B9207-015 in beagle dogs following inhalation for 12 months                                                                            | 116/96    |
| Histologic evaluation of the nasal turbinates - Comparison of 5 different dog studies                                                              | 117D/98K1 |
| Toxicokinetics of ciclesonide and metabolite B9207-021 in a 1-year inhalation toxicity study in beagle dogs (aerosol generated from powder)        | 221/97    |
| Toxicity of B9207-015 in beagle dogs following oral administration for 4 weeks                                                                     | 75/94     |
| Pharmacokinetics of ciclesonide and its metabolite B9207-021 in a 4-week oral toxicity study in dogs                                               | 183/96    |
| Toxicity of B9207-015 in beagle dogs following oral administration for 12 months                                                                   | 136/98    |
| Toxicokinetics of ciclesonide and metabolite B9207-021 in a 1-year oral toxicity study in beagle dogs                                              | 238/98    |
| Pathology peer and pathology review working group (PWG) review of the testes from male dogs from six preclinical toxicity studies with ciclesonide | 145/2003  |
| Hemolytic potential of B9207-015 in beagle dogs following short-term intravenous administration                                                    | 33/95     |
| The toxicity of B9207-015 in beagle dogs following intravenous administration for 2 weeks per infusionem                                           | 154/94    |
| Pharmacokinetics of ciclesonide and its metabolite B9207-021 in a 2-week intravenous toxicity study in dogs                                        | 155/96    |
| <b>Genotoxicity</b>                                                                                                                                |           |
| Reverse mutation test of ciclesonide in bacteria                                                                                                   | 44E/99    |
| Chromosome aberration assay in human lymphocytes in vitro with B9207-015                                                                           | 111/94    |
| Action of B9207-015 on mutations affecting the hypoxanthine-guanine phosphoribosyl transferase locus in V79 cells (HPRT test)                      | 209/95    |
| Micronucleus test with V79 cells in vitro with B9207-015 (mitotic-shake-off-method)                                                                | 80/97     |
| Testing of B9207-015 for mutagenic activity in the mouse by means of the micronucleus test                                                         | 100/95    |
| Testing of B9207-015 for mutagenic activity in the mouse by means of the micronucleus test (second study)                                          | 161/95    |
| Testing of B9207-015 for mutagenic activity in the mouse by means of the micronucleus test with oral administration (third study)                  | 161/96    |
| Mouse micronucleus test: Comparison between ciclesonide, budesonide and dexamethasone with oral administration                                     | 75/96     |
| <b>Carcinogenicity</b>                                                                                                                             |           |
| (Ciclesonide) – carcinogenicity study by oral gavage administration to B6C3F1 mice for 104 weeks                                                   | 281/2000  |
| Toxicokinetics of ciclesonide in an oral carcinogenicity study in mice                                                                             | 282/2000  |

|                                                                                                                                                           |          |
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| Carcinogenicity inhalation study of B9207-015 in metered dose inhaler (MDI) in wistar (WU) rats                                                           | 176/99   |
| Toxicokinetics of ciclesonide in an inhalative carcinogenicity study in wistar rats (aerosol generated from metered dose inhalers)                        | 177/99   |
| The toxicity of B9207-015 after oral administration in the mouse for 3 months (dose range finding)                                                        | 185/95   |
| The toxicity of B9207-015 after oral administration in the mouse for 3 months (dose range finding, second study)                                          | 20/97    |
| <b>Reproductive and developmental toxicity</b>                                                                                                            |          |
| Influence on male and female fertility (rat). Effects on early embryo-fetal development. Toxicity of B9207-015 for reproduction after oral administration | 153/97   |
| Toxicity of B9207-015 for reproduction after oral administration. Study for effects on embryo-fetal development in the rat.                               | 109/95   |
| Toxicity of B9207-015 for reproduction. Study for effects on embryo-fetal development in the rabbit s.c.                                                  | 106/95   |
| Toxicity of B9207-015 for reproduction. Study for effects on embryo-fetal development in the rabbit after subcutaneous administration                     | 283/99   |
| Ciclesonide: Study for effects on pre- and postnatal development including maternal function in the rat                                                   | 235/2000 |
| <b>Local tolerance</b>                                                                                                                                    |          |
| Study on primary irritation of B9207-015 in the guinea pig                                                                                                | 123/94   |
| Local toxicity of B9207-015 after a single intravenous, paravenous or intra-arterial injection in the rabbit                                              | 72/95    |
| <b>Other toxicity studies</b>                                                                                                                             |          |
| Test for sensitizing properties of B9207-015 in the guinea pig                                                                                            | 122/94   |
| Antigenicity study of ciclesonide in guinea pigs (ASA, PCA reaction)                                                                                      | 48E/99   |
| Antigenicity study of ciclesonide in mice-rats (PCA reaction)                                                                                             | 49E/99   |
| 28-day endocrine toxicity study in rats treated with B9207-015 by inhalation                                                                              | 59/2001  |
| Ciclesonide – Subchronic toxicity in the rat after subcutaneous administration (28 days)                                                                  | 112E/94  |
| Ciclesonide – Chronic toxicity in the rat after subcutaneous administration (6 months)                                                                    | 113E/94  |
| Ciclesonide – Subchronic toxicity in the dog after inhalation (28 days)                                                                                   | 114E/94  |
| Ciclesonide – Chronic toxicity in the dog after inhalation (6 months)                                                                                     | 115E/94  |
| Assessment of mutagenic potential in histidine auxotrophs of Salmonella typhimurium (Ames Test)                                                           | 107E/94  |
| Influence of B9207-015 on erythrocyte stability in vitro                                                                                                  | 8/95     |

**Studies not reviewed in this submission (not relevant to the proposed indication or redundant to the studies having been reviewed)**

|                                                                         |  |
|-------------------------------------------------------------------------|--|
| <b>Pharmacokinetics</b>                                                 |  |
| <b>Analytical methods and validation report</b>                         |  |
| Validation of a LC/MS/MS method for the assay of ciclesonide metabolite |  |

|                                                                                                                                                                                                                                                                                            |          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| (B9207-021) in mouse serum                                                                                                                                                                                                                                                                 |          |
| Cross-validation of a LC/MS/MS method for the measurement of the ciclesonide metabolite (B9207-021) in mouse serum.                                                                                                                                                                        | 55/2000  |
| Validation of a LC/MS/MS method for the assay of ciclesonide metabolite (B9207-021) in rat serum and cross-validation in rat plasma                                                                                                                                                        | 196E/97  |
| Set-up and validation of a LC/MS/MS method for the measurement of the ciclesonide metabolite (B9207-021) in rat serum                                                                                                                                                                      | 173E/99  |
| Set-up and validation of a LC/MS/MS method for the measurement of the ciclesonide metabolite (B9207-021) in rabbit serum                                                                                                                                                                   | 56/2000  |
| Validation of the analytical procedure for the determination of ciclesonide (B9207-015) and metabolite (B9207-021) in dog plasma using automated solid phase extraction and HPLC with mass spectrometry detection                                                                          | 154E/96  |
| Cross-validation of the analytical procedure for the determination of ciclesonide (B9207-015) and metabolite (B9207-021) in dog serum with the fully validated dog plasma method using automated solid phase extraction and liquid chromatography with tandem mass spectrometric detection | 183E/97  |
| Stability of B9207-021 in rat and mouse serum at -20°C for 6 and 12 months. (Amendment to: Validation of a LC/MS/MS method for the assay of ciclesonide metabolite (B9207-021) in rat and mouse serum)                                                                                     | 174E/99  |
| Investigation into the storage stability of ciclesonide (B9207-015) and metabolite (B9207-021) in incurred human serum and dog plasma samples stored at nominal -20 degrees C° using automated solid phase extraction and liquid chromatography with tandem mass spectrometry detection    | 175E/99  |
| Set-up and feasibility of a LC/MS/MS method for the simultaneous, isotope specific determination of [12C/14C]-ciclesonide metabolite (B9207-021) and [12C/14C]-ciclesonide (B9207-015) in rabbit plasma, rat, mouse and dog serum containing esterase inhibitor                            | 91/2003  |
| Validation of a LC/MS/MS method for the determination of ciclesonide and ciclesonide metabolite in dog serum                                                                                                                                                                               | 152/2004 |
| Long term stability of ciclesonide and ciclesonide metabolite in dog serum                                                                                                                                                                                                                 | 153/2004 |
| <b>Pharmacology</b>                                                                                                                                                                                                                                                                        |          |
| Ciclesonide: in-vitro pharmacology evaluation                                                                                                                                                                                                                                              | 29/2001  |
| <b>Pharmacokinetics</b>                                                                                                                                                                                                                                                                    |          |
| Pharmacokinetics of [14C]-ciclesonide in the mouse: Serum concentrations of total radioactivity, ciclesonide and metabolite B9207-021 after a single oral and intravenous dose                                                                                                             | 194/99   |
| Pharmacokinetic, radiokinetic and [14C] excretion/mass balance study of ciclesonide in male B6C3F1 mice                                                                                                                                                                                    | 94/2003  |
| Pharmacokinetics of metabolite B9207-021 in a single intravenous and single oral dose study in male mouse with ciclesonide                                                                                                                                                                 | 59/2000  |
| Balance excretion and pharmacokinetic study of [14C]-ciclesonide in the rat                                                                                                                                                                                                                | 121/96   |
| Pharmacokinetic, radiokinetic and [14C] excretion/mass balance study of ciclesonide in male wistar rats                                                                                                                                                                                    | 92/2003  |
| Pharmacokinetics of metabolite B9207-021 in a single intravenous and single oral dose study in male rats with ciclesonide                                                                                                                                                                  | 58/2000  |
| Pharmacokinetics of metabolite B9207-021 in a ciclesonide single dose inhalation study in rats                                                                                                                                                                                             | 240/99   |

|                                                                                                                                                           |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Pharmacokinetics of metabolite B9207-021 in a 4-week ciclesonide inhalation study in Wistar rats                                                          | 245/2000  |
| Pharmacokinetic, radiokinetic and [14C] excretion/mass balance study of ciclesonide in female himalayan rabbits                                           | 96/2003   |
| Pharmacokinetic, radiokinetic and [14C] excretion/mass balance study of ciclesonide in male beagle dogs                                                   | 98/2003   |
| Indirect assessment of the bioavailability of B9207-015 in the dog via determination of the level of endogenous cortisol                                  | 36/95     |
| Pharmacokinetics and pharmacodynamics of the steroidal antiinflammatory drug ciclesonide and budesonide in dogs after intravenous and oral administration | 102E/95K1 |
| <b>Distribution</b>                                                                                                                                       |           |
| Serum protein binding of ciclesonide in different species, including humans                                                                               | 246/2001  |
| RPR 257970: Plasma protein binding in different species, blood cell/plasma partitioning in human blood and drug interaction in human plasma               | 79/2001   |
| Ciclesonide: RPR 257970 protein binding in plasma of various species and in isolated human plasma proteins                                                | 103/2003  |
| <b>Metbolism</b>                                                                                                                                          |           |
| Metabolism of ciclesonide in the mouse following a single oral or intravenous administration of [14C] Ciclesonide                                         | 95/2003   |
| Metabolism of ciclesonide in the rat following a single oral or intravenous administration of [14C] ciclesonide                                           | 93/2003   |
| The metabolism of [14C]-ciclesonide in the rat                                                                                                            | 252/99K1  |
| The metabolism of [14C]-ciclesonide in the rat: metabolite patterns in plasma and selected tissues after ethanolic extraction                             | 62/2001   |
| Formation of fatty acid conjugates of B9207-021 in the rat lung in a 4-week ciclesonide inhalation study                                                  | 106/2001  |
| Metabolism of ciclesonide in the rabbit following a single oral or intravenous administration of [14C] ciclesonide                                        | 97/2003   |
| Metabolism of ciclesonide in the dog following a single oral or intravenous administration of [14C] ciclesonide                                           | 99/2003   |
| Comparative in vitro metabolism of [14C]-ciclesonide in hepatocytes from mice, rats, rabbits and dogs                                                     | 137/2003  |
| Structure of the major in vitro metabolites M2, M3 family and M5 of ciclesonide                                                                           | 240/98    |
| A study of the hydrolysis of ciclesonide to M1 by rat and human tissues                                                                                   | 104/2003  |
|                                                                                                                                                           |           |
| Ciclesonide: absorption, distribution and excretion study in the rat                                                                                      | 88E/94    |
| Ciclesonide: absorption and excretion study in the dog                                                                                                    | 85E/94    |
| Pharmacokinetic study of ciclesonide. Urinary, fecal and expiratory excretion in rats after single intravenous administration of [14C]-Ciclesonide        | 101/2003  |
| Pharmacokinetics of ciclesonide and its metabolite B9207-021 in a sighting per inhalation toxicity study (DRF) in dogs                                    | 184/96    |
| Toxicokinetics of ciclesonide and metabolite B9207-021 in a 4-week inhalation toxicity study in beagle dogs (aerosol generated from a MDI)                | 165/97    |
| Corticosterone in plasma of rats following inhalation of B9207-015                                                                                        | 189E/97   |
| Pharmacokinetics of metabolite B9207-021 in a 2-week subcutaneous study in male rats with ciclesonide (R15/FKM/110)                                       | 165/2001  |
| Assessment of pulmonary selectivity of ciclesonide prodrug and metabolite powders using an ex-vivo receptor binding assay in rats                         | 75/2001   |

2. Ciclesonide inhibits IL-1 $\beta$  induced IL-8 release in human nasal epithelial cells ( $EC_{50}$ =0.81 nM) and bronchial epithelial cells ( $EC_{50}$ =0.46-3.14 nM). Details can be found in the review #7 for IND 65,488 submission of 10/25/2005).
3. Ciclesonide prevents symptoms of ovalbumin-induced allergic rhinitis in guinea pigs in a dose related manner. Ciclesonide at 10 ug/nostril prevented 93% of the induced increase in nasal respiratory resistance and 99% of the increase in eosinophils in nasal lavage fluid (original review for IND 65,488 submission of 8/8/2002).

### 2.6.2.3 Secondary pharmacodynamics

1. Anti-inflammatory effects: Ciclesonide inhibits accumulation of inflammatory cells (neutrophils and eosinophils) and protein in the lower airway, and reduces lung edema in rat allergic lung inflammation models, inhibits bradykinin induced mucosal leakage in rat trachea in situ, reduces croton oil induced mouse ear edema and inhibits granuloma formation in response to subcutaneous cotton implantation.
2. Ciclesonide inhibits PDGF-induced airway smooth muscle cell proliferation (Study report 69/2005)  
Study report 69/2005: primary human airway smooth muscle cells were incubated for 12 hours with various steroids and then platelet derived growth factor (PDGF, 10 ng/mL). Cell proliferation was determined by measuring  $^3$ H-thymidine incorporation. Ciclesonide showed similar efficacy but lower potency compared with fluticasone and budesonide ( $EC_{50}$  value was 0.088, 0.32, and 6.0 nM for fluticasone, budesonide and ciclesonide, respectively) when cells were incubated with steroids for 24 hours; Ciclesonide and its active metabolite, RM-1 showed slightly higher potency than fluticasone and budesonide (at 10nM concentration, inhibition was 13%, 30%, 0%, 0% for RM-1, Ciclesonide, budesonide and fluticasone, respectively) when the proliferation was measured at 24 hours of culture with the steroid exposures in the first 12 hours only.
3. Ciclesonide is less potent than fluticasone in anti-inflammatory effects (lung eosinophilia and edema), bronchio-hyperresponsiveness in an allergic lung inflammation model, as well as typical glucocorticoid side effects (thymus and adrenal atrophy, etc) as detailed below (Study reports 28/2001 and 160/2003).

#### Ciclesonide is less potent than fluticasone in inhibiting lung inflammation and typical steroid side effects (Study Report 28/2001):

1). Ciclesonide and RM-1 are less potent than fluticasone in inhibiting antigen-induced pulmonary eosinophilia: In ovalbumin sensitized rats, intratracheal administration of ciclesonide (0.1-1.0 mg/kg, 24 h and 1 h before antigen challenge), RM-1 (0.3-10 mg/kg) or Fluticasone (0.03-1 mg/kg) all showed inhibition of lung eosinophilia. The inhibition of Ciclesonide was 7.2-7.9 fold less potent than fluticasone and the inhibition of RM-1 was 2-2.6 fold less active than the parent compound.

2). Ciclesonide and RM-1 are less potent than fluticasone on the inhibition of Sephadex-induced lung edema: Intratracheal administrations of Ciclesonide, RM-1 and Fluticasone at 24 h before and together with the i.t. administration of Sephadex in rats, resulted in an inhibition of Sephadex-induced increase of lung wet weight in a dose related manner. The EC<sub>50</sub> value of this effect was 0.72, 1.08 and 0.08 mg/kg for ciclesonide, RM-1 and fluticasone, respectively. Thus, ciclesonide and its active metabolite are both less potent than fluticasone in this respect.

3). Ciclesonide and RM-1 are less potent in causing typical glucocorticoid side effects than fluticasone: Rats received 7 days of intratracheal administration of ciclesonide, RM-1 and Fluticasone and were compared on the changes in body weights, thymus involution, adrenal involution, osteopenia of femoral growth plate and serum osteocalcin. The potency of the side effects was fluticasone>RM-1>ciclesonide (see the table below)

Summary of side-effects of 7 days i.t. administration of test compounds

| Compound           | Change in body weight gain            | Thymus involution                     | Adrenal involution                    | Growth Plate                          | Serum Osteocalcin                     |
|--------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
|                    | ED <sub>50</sub><br>(mg/kg/day, i.t.) | ED <sub>50</sub><br>(mg/kg/day, i.t.) | ED <sub>25</sub><br>(mg/kg/day, i.t.) | ED <sub>20</sub><br>(mg/kg/day, i.t.) | ED <sub>20</sub><br>(mg/kg/day, i.t.) |
| <b>Ciclesonide</b> | 0.2                                   | 0.32                                  | 3.11                                  | 0.87                                  | 2.98                                  |
| <b>RM-1</b>        | 0.09                                  | 0.16                                  | 0.99                                  | 0.09                                  | 5.89                                  |
| <b>Fluticasone</b> | 0.02                                  | 0.05                                  | 0.07                                  | 0.04                                  | 0.36                                  |

Ciclesonide is less potent than fluticasone on inhibition of allergen-induced chronic airway inflammation and bronchial hyperresponsiveness (Study report 160/2003):

In OVA sensitized rats, intratracheal administration of ciclesonide (0.01-0.1 mg/kg) or fluticasone (0.01-0.1 mg/kg) twice per day on each of 6 OVA challenge days (Days 6, 9, 12, 15, 18 and 21 post the first sensitization dose), resulted in suppression of the following: bronchio-hyperresponsiveness (BHR), goblet cell hyperplasia, airway smooth muscle cells and airway epithelial cells proliferation, as well as reduced eosinophil infiltration. On all of these effects, ciclesonide is less potent than fluticasone (see the details below).

| Treatment          | BHR (PC100) <sup>1</sup> | Goblet <sup>2</sup> | BrdU <sup>+</sup> ASM cells % <sup>3</sup> | BrdU <sup>+</sup> AE cells <sup>4</sup> | Eosinophils (MBP <sup>+</sup> ) <sup>5</sup> | T cells |
|--------------------|--------------------------|---------------------|--------------------------------------------|-----------------------------------------|----------------------------------------------|---------|
| Nonsensitized      | 1.91                     | 9.94                | 1.11                                       | 15.1                                    | 17.7                                         | 19.0    |
| Vehicle            | 2.46                     | 17.9                | 3.05                                       | 33.8                                    | 32.7                                         | 34.5    |
| Cic. 0.01 mg/kg    |                          | 11.0                | 0.93                                       | 15.0                                    | 17.3                                         | 21.3    |
| Cic. 0.03 mg/kg    | 1.28                     | 11.5                | 0.86                                       | 15.4                                    | 16.8                                         | 20.8    |
| Cic. 0.1 mg/kg     | 1.74                     | 10.9                | 0.78                                       | 12.3                                    | 13.1                                         | 20.4    |
| Flutic. 0.01 mg/kg |                          |                     | 0.85                                       | 15.3                                    | 16.0                                         | 19.3    |
| Flutic. 0.03 mg/kg |                          | 11.8                | 0.7                                        | 13.3                                    | 15.0                                         | 18.5    |
| Flutic. 0.1 mg/kg  |                          | 5.4                 | 0.7                                        | 9.42                                    | 5.2                                          | 11.2    |

<sup>1</sup> -log concentration of Ach required to increase baseline resistance by 100%. Lung resistance was measured by plethysmography at 18-24 hours after final OVA challenge.

<sup>2</sup> Expressed as cells/m<sup>2</sup> basement membrane of airway

<sup>3</sup> Number of BrdU positive cells was detected by an immunohistochemistry method and expressed as % of ASM cells (airway smooth muscle cells). BrdU was intraperitoneally administered twice on each of challenge day (0 h and 8-12 hours after challenge).

<sup>4</sup> AE cells- Airway epithelial cells

<sup>5</sup> Major basic protein, as an indicator of eosinophils was detected by an immunohistochemistry method and expressed as cells/m<sup>2</sup> basement membrane.

<sup>6</sup> CD2<sup>+</sup> T cells/m<sup>2</sup> basement membrane

#### **2.6.2.4 Safety pharmacology**

No additional safety pharmacology data were submitted. All safety pharmacology studies were reviewed under NDA — There were no remarkable findings in safety pharmacology studies in CNS, cardiovascular and respiratory systems, and renal function.

#### **2.6.2.5 Pharmacodynamic drug interactions**

The combination of Ciclesonide or RM-1 with Azelastine (antihistamine) showed a trend of synergistic effects of inhibition of cytokine release (TNF $\alpha$ , IL-6, MCP-1 and RANTES) from human monocytes in response to LPS (lipopolysaccharide) (see review #7 for IND 65,488 submission dated 10/25/2005).

### **2.6.3 PHARMACOLOGY TABULATED SUMMARY**

Not applicable because no relevant information is available.

### **2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

#### **2.6.4.1 Brief summary**

Due to an extensive first pass effect, oral bioavailability 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 T<sub>1/2</sub> of ciclesonide was short (1 hour in rats and mice) which is probably due to conversion of ciclesonide to RM-1. T<sub>1/2</sub> 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.

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 T<sub>1/2</sub> = 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, 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 (C<sub>max</sub> and AUC), no drug accumulation over 26 weeks and no gender related differences noted.

#### **2.6.4.2 Methods of Analysis**

Ciclesonide and its metabolites were determined with LC/MS/MS and liquid scintillation counting was used for radioactivity measurement when radioactive labeled drug was administered. The lower limit of quantification was 250 pg/mL for rat and mouse samples and 25 pg/mL for dog samples.

#### **2.6.4.3 Absorption**

No additional data were submitted. Ciclesonide absorption data were submitted and reviewed under [REDACTED]. Following an oral dose, ciclesonide is rapidly absorbed and metabolized to inactive forms. The bioavailability of combined ciclesonide and the active metabolite (RM-1) is less than 6% in most animal species suggesting a pronounced first-pass effect.

#### **2.6.4.4 Distribution**

No additional data were submitted. Ciclesonide distribution data were reviewed under [REDACTED]. After absorption, ciclesonide is widely distributed in the body including lung, heart, thyroid, liver, and kidney. Minimal amounts were found in fetuses and milk after administration to pregnant rats. Plasma protein binding is about 99% in rat, dog and human sera.

#### **2.6.4.5 Metabolism**

1. Overall metabolism: The absorbed ciclesonide is rapidly de-esterified into the active metabolite RM-1 and which is further metabolized. In human studies, RM-1 was the major circulating metabolite. The glucocorticoid receptor binding affinities of all metabolites from RM-1 were significantly reduced compared to that of RM-1. There are no qualitative differences in the metabolism of ciclesonide across different species including humans. A quantitative comparison among different species for the metabolites was not obtained as there were no appropriate studies designed for such a purpose. The details of the above data can be found in the review for [REDACTED].
2. Nasal mucosal metabolism: Studies using human nasal epithelial cells and rabbit nasal mucosa indicated that ciclesonide is metabolized in those cells or tissue to RM-1 and M4 (fatty acid conjugates of RM-1). The rate of metabolism is quick (RM-1



|                                        | 1h   | 3h   | 6h   | 16h  |
|----------------------------------------|------|------|------|------|
| <b>ASMC's</b>                          |      |      |      |      |
| Ciclesonide [ $\mu\text{mol/l}$ ]      | 0.25 | 0.18 | 0.11 | BLQ  |
| Des-CIC [ $\mu\text{mol/l}$ ]          | 0.11 | 0.26 | 0.39 | 0.55 |
|                                        |      |      |      |      |
| <b>Primary airway epithelial cells</b> |      |      |      |      |
| Ciclesonide [ $\mu\text{mol/l}$ ]      | 0.31 | 0.22 | 0.16 | BLQ  |
| Des-CIC [ $\mu\text{mol/l}$ ]          | 0.12 | 0.23 | 0.39 | 0.59 |

BLQ -> Below Limit of Quantification. —

Table 3: Concentrations of ciclesonide and des-CIC in supernatant of ASMC's or airway epithelial cells. Starting concentration was — ciclesonide, which was completely converted into its active metabolite within 16 hours. Airway epithelial cells exhibited no significant different conversion rate.

In conclusion, ciclesonide is slowly metabolized in human airway smooth muscle and airway epithelial cells. The study with airway smooth muscle cells showed a slow onset but a long lasting GR activation (24 hours) which is similar to budesonide but longer than fluticasone (6 hours).

Study Report 239/2002 – Comparison of the concentrations of ciclesonide and its metabolite in rabbit nasal tissues after intranasal administration of ciclesonide suspensions in hypotonic (glucose-free) and isotonic (glucose-contained) ciclesonide nasal spray formulations:

This study was conducted to test the hypothesis that use of the hypotonic ciclesonide nasal spray formulation could improve the retention and reduce the dosage for the same pharmacological effects compared to the isotonic formulation.

Following a single dose (143 ug/animal, 100 uL/nostril) intranasal administration of ciclesonide to rabbits, the mean nasal mucosal concentrations of RM-1 were higher in the group that received a hypotonic suspension compared with the group received the isotonic suspension at all sampling points (approximately 6, 12, 14-fold at 0.5, 2 and 4 hours, respectively). Similar to RM-1, the ciclesonide concentration was also higher in rabbits that received the hypotonic formulation at all time points; approximately 25, 34, and 16-fold at 0.5, 2 and 4 hours, respectively. However, statistical significance was reached at 4 hours only.

#### 2.6.4.6 Excretion

No additional excretion data were submitted. Excretion data reviewed under — indicates that the oral and intravenous doses of ciclesonide are eliminated primarily via feces (81-82% of dose) and a small amount was via urine (8-9% of dose). No information regarding inhalation administration is available.

#### 2.6.4.7 Pharmacokinetic drug interactions

No additional data were submitted. Pharmacokinetic drug interaction data were reviewed under [redacted]. Ciclesonide has no significant inductive or inhibitory effects on P450 enzymes (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4).

#### 2.6.4.8 Other Pharmacokinetic Studies

There are no relevant data provided.

#### 2.6.4.9 Discussion and Conclusions

Most pharmacokinetic data were submitted and reviewed under [redacted]. 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 T<sub>1/2</sub> of ciclesonide was short (1 hour in rats and mice) which is probably due to conversion of ciclesonide to RM-1. T<sub>1/2</sub> of RM-1 was 2.4 to 7 hours in rats, mice, rabbits, and dogs.

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 is similar among the animal species studied (ciclesonide T<sub>1/2</sub> = 1-2 hours in nasal mucosa homogenates from rats, rabbits, guinea pigs 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. 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.

Toxicokinetic data were not obtained in rat intranasal studies (14-Day and 28-Day, 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 (C<sub>max</sub> and AUC), no drug accumulation over 26 weeks and no gender related differences noted.

Additionally, a study in rabbits demonstrating higher nasal mucosal concentrations of ciclesonide and RM-1 after administration of a hypotonic formulation compared to an isotonic formulation suggested that a lower administered dosage would be needed using the hypotonic nasal spray formulation (glucose free) to obtain similar pharmacological effects.

A study less relevant to intranasal use of this drug, showed that the metabolic rate of ciclesonide in human airway epithelial and smooth muscle cells was slow (RM-1 was not detected until after 6 hours of incubation).

### 2.6.4.10 Tables and figures to include comparative TK summary

There were no plasma TK data available for rat intranasal studies (up to 429 ug/kg) because plasma levels were all below quantification limit of 0.25 ng/mL. Dog TK data were obtained (300-4800 mcg/body) and suggest that dogs have higher systemic absorption than rats at the tested doses. Dog intranasal studies of 14-day, 28-day and 26-week durations revealed similar profiles. Drug exposures (C<sub>max</sub> and AUC) increased in proportion to the doses and there was no significant drug accumulation over 26 weeks of dosing. There were also no gender related differences noted. The table below summarizes the dog TK data from a 26-week intranasal study.

Pharmacokinetic parameters in the beagle 26-week intranasal study

| Dose<br>(ug/body)                                     | Day 0                   |                             |                                   | Week 13                 |                             |                                   | Week 26                 |                             |                                   |
|-------------------------------------------------------|-------------------------|-----------------------------|-----------------------------------|-------------------------|-----------------------------|-----------------------------------|-------------------------|-----------------------------|-----------------------------------|
|                                                       | T <sub>max</sub><br>(h) | C <sub>max</sub><br>(pg/mL) | AUC <sub>0-24h</sub><br>(pg.h/mL) | T <sub>max</sub><br>(h) | C <sub>max</sub><br>(pg/mL) | AUC <sub>0-24h</sub><br>(pg.h/mL) | T <sub>max</sub><br>(h) | C <sub>max</sub><br>(pg/mL) | AUC <sub>0-24h</sub><br>(pg.h/mL) |
| Ciclesonide (B9207-015) in male beagles               |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 0.5                     | 185                         | 259                               | 2.8                     | 203                         | 736                               | 1.2                     | 163                         | 268                               |
| 1200                                                  | 0.8                     | 192                         | 324                               | 0.9                     | 391                         | 588                               | 0.7                     | 274                         | 525                               |
| 4800                                                  | 0.8                     | 930                         | 1703                              | 0.4                     | 875                         | 3357                              | 0.7                     | 1044                        | 2574                              |
| Ciclesonide (B9207-015) in female beagles             |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 1.3                     | 233                         | 527                               | 1.0                     | 112                         | 278                               | 0.8                     | 166                         | 198                               |
| 1200                                                  | 0.9                     | 441                         | 641                               | 1.3                     | 306                         | 536                               | 1.1                     | 367                         | 698                               |
| 4800                                                  | 0.6                     | 648                         | 1360                              | 1.2                     | 1017                        | 3068                              | 1.2                     | 988                         | 2375                              |
| Ciclesonide metabolite (B-9207-021) in male beagles   |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 1.4                     | 145                         | 302                               | 1.0                     | 169                         | 484                               | 1.5                     | 136                         | 436                               |
| 1200                                                  | 1.8                     | 184                         | 827                               | 1.8                     | 333                         | 1549                              | 1.5                     | 218                         | 1011                              |
| 4800                                                  | 0.9                     | 1012                        | 4519                              | 1.3                     | 1082                        | 6744                              | 1.1                     | 1131                        | 5970                              |
| Ciclesonide metabolite (B-9207-021) in female beagles |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 1.5                     | 102                         | 289                               | 1.5                     | 113                         | 273                               | 1.3                     | 164                         | 332                               |
| 1200                                                  | 0.9                     | 298                         | 1005                              | 1.3                     | 270                         | 1152                              | 1.4                     | 361                         | 1423                              |
| 4800                                                  | 0.8                     | 722                         | 3517                              | 1.3                     | 1128                        | 5440                              | 1.2                     | 1204                        | 5591                              |

### 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable because no relevant data were provided.

### 2.6.6 TOXICOLOGY

#### 2.6.6.1 Overall toxicology summary

##### General toxicology:

Based on the systemic toxicity data obtained in the inhalation program \_\_\_\_\_, the Division agreed that a bridging toxicology program consisting of up to 6 month intranasal toxicology study in an appropriate species would satisfy the preclinical requirements for the current NDA. 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 [redacted] 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 these 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 [redacted]

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  $AUC_{0-24h}$  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 $\mu\text{g}/\text{cm}^2$ | Safety margin <sup>b</sup> | 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 <sup>a</sup> , 1200 <sup>a</sup> , 4800 <sup>a</sup> | 1200 <sup>a</sup> | 5.43                                              | 4.3                        | 103/2004  |
| Human <sup>c</sup> | -               | 200 $\mu\text{g}$                                        | -                 | 1.25                                              | -                          | -         |

<sup>a</sup>. ug/dog; <sup>b</sup>. 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  $\text{cm}^2$  in humans, dogs, and rats, respectively, and assuming body weights of 250 g for rats and 10 kg for dogs; <sup>c</sup>. Proposed maximum clinical dose

Details of the studies can be found in the attached reviews for IND 65,488: submissions dated 8/8/2002 (Report Nos. 218/2001, 11/2001, 219/2001 and 16/2002) and 10/14/2004 (Report 103/2004).

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 \_\_\_\_\_ (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 \_\_\_\_\_ Two-year carcinogenicity studies were conducted in mice by oral gavage at doses of 150, 450 and 900  $\mu\text{g}/\text{kg}$  and in rats by inhalation at delivered doses of 30, 76 and 193  $\mu\text{g}/\text{kg}$ . Ciclesonide did not increase any tumor incidences in mice and rats.

Reproductive toxicology: Studies regarding the reproductive toxicity of ciclesonide were reviewed under \_\_\_\_\_

Ciclesonide does not affect fertility, embryofetal 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  $\mu\text{g}/\text{kg}$ ) resulted in post-implantation loss and reduced litter weight at doses of 100  $\mu\text{g}/\text{kg}$  and above. There were no living fetuses in the 400  $\mu\text{g}/\text{kg}$  dose group. Fetal weights were reduced at doses of 25  $\mu\text{g}/\text{kg}$  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 \_\_\_\_\_ 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

Single dose intranasal studies were not conducted. Single dose studies conducted by other routes (intraperitoneal injection and oral gavage) have been reviewed under \_\_\_\_\_. The minimum lethal doses in mice and rats were 200 mg/kg by intraperitoneal treatment 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.

#### 2.6.6.3 Repeat-dose toxicity

Under the current NDA submission, the sponsor provided supplemental data to the previously conducted rat 28-day intranasal study (CLE Study 0792/017, reviewed under IND 65,488 original submission). The previously conducted 28-day intranasal study (CLE study 0792/017) in rats revealed no local toxicity. Systemic toxicities included a slight body weight decrease, increased blood triglyceride levels in females (males were not examined) and testicular atrophy. The testicular atrophy was considered not treatment related because it was not observed in the studies with higher systemic drug exposures and similar or longer treatment durations. Recovery data were collected for body weight and blood chemistry only. The increase of triglyceride was reversible after 4-week of recovery period.

The current study (see below) was conducted to obtain clinical chemistry data not obtained in error during the previous 4-week toxicity study in this species. Also, the reversibility of any effects observed in the current study was then assessed over 28 day treatment free period.

**Study title:** Ciclesonide nasal spray: 28 day nasal administration toxicity study in the male rat with a 28 day treatment-free period

**Key study findings:** This study provided supplemental data (blood chemistry) to the previously conducted 4-week study. There was no drug-related finding observed in this study in regard to behavior and appearance, body weight, food consumption, clinical chemistry.

**Study no.:** \_\_\_\_\_ No. 0792/018, Study report No. 49/2003

**Volume #, and page #:** E-submission

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** 10/22/01

**GLP compliance:** Yes

**QA report:** yes (X) no ( )

**Drug, lot #, and % purity:** Ciclesonide nasal spray, CIN-010807-S77, purity \_\_\_\_\_  
CIN-010808-S78, purity \_\_\_\_\_ : CIN-010809-S79, purity \_\_\_\_\_

## Methods

Study design was the same as that used in the previous 4-week study (CLE Study 0792/017) and is presented as the following:

| Group No | Test article                                              | Group Description    | Dose level (per day)# |            | Animals numbers |                      |
|----------|-----------------------------------------------------------|----------------------|-----------------------|------------|-----------------|----------------------|
|          |                                                           |                      | (mcg/animal)          | (mcg/kg)\$ | Main study      | Treatment-free phase |
| 1        |                                                           | Physiological saline | 0                     | 0          | 10              | -                    |
| 2        | Ciclesonide Nasal Spray (Glucose-free, 0 mcg/actuation)   | Vehicle Control      | 0                     | 0          | 10              | 6                    |
| 3        | Ciclesonide Nasal Spray (Glucose-free, 50 mcg/actuation)  | Low                  | 21.4                  | 107        | 10              | -                    |
| 4        | Ciclesonide Nasal Spray (Glucose-free, 100 mcg/actuation) | Intermediate         | 42.8                  | 214        | 10              | -                    |
| 5        | Ciclesonide Nasal Spray (Glucose-free, 200 mcg/actuation) | High                 | 85.7                  | 429        | 10              | 6                    |

# Animals received two instillations per day of approximately 15  $\mu$ L per actuation. Total volume given per day was nominally 30  $\mu$ L. Each nostril was dosed once daily

\$ Dosages were calculated from the nominal concentration and expected total dose volume assuming a nominal weight of 200 g per animal (e.g. dosage [Group 5] = 30  $\mu$ L x 2.857  $\mu$ g/ $\mu$ L + 0.20 kg)

1 0.9% physiological saline supplied by \_\_\_\_\_

## Results:

Examinations on behavior and appearance, body weight, food consumption, clinical chemistry resulted in no remarkable finding after 28 days of treatment. Recovery study revealed no remarkable findings as well.

#### 2.6.6.4 Genetic toxicology

No additional data were submitted. Genotoxicity studies were reviewed under [REDACTED]. Ciclesonide was negative in an Ames test, chromosome aberration assay in human peripheral lymphocyte, CHO/HGPRT forward mutation assay, an in vitro micronucleus test in V79 cells, but was positive in an in vivo mouse micronucleus test.

#### 2.6.6.5 Carcinogenicity

No additional data were submitted. Ciclesonide carcinogenicity studies were reviewed under [REDACTED]. 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.

#### 2.6.6.6 Reproductive and developmental toxicology

No additional data were submitted. Studies for reproductive and developmental toxicities were reviewed under [REDACTED].

Ciclesonide does not affect fertility, or embryofetal development as tested in rats at oral doses up to 0.9 mg/kg. 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 100 µg/kg and above. There were no living fetuses in 400 µg/kg. Fetal weights were reduced at 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 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 of 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.

Prenatal and postnatal development study revealed no ciclesonide treatment related effects in the rat with oral doses up to 0.9 mg/kg.

#### 2.6.6.7 Local tolerance

Study title: Primary eye irritation study of ciclesonide nasal spray in rabbits (Study report 344/2003)

Summary of the study:

This GLP study was guided by OECD guidance to evaluate the irritability of Ciclesonide nasal spray to the eyes. Ciclesonide clinical formulations were used in this study. Three rabbits/group were given a single dose, 0.1 mL of ciclesonide nasal spray formulations at strength of 25 ug/actuation or 100 ug/actuation. The study design was the following:

| Group | Eye Examined | Treatment                             | Washing | Number of Animals<br>(Animal No.) |
|-------|--------------|---------------------------------------|---------|-----------------------------------|
| 1     | Right        | Ciclesonide Nasal Spray <sup>a)</sup> | -       | 3 (1 – 3)                         |
|       | Left         | No Treatment                          | -       |                                   |
| 2     | Right        | Ciclesonide Nasal Spray <sup>a)</sup> | +       | 3 (4 – 6)                         |
|       | Left         | No Treatment                          | +       |                                   |
| 3     | Right        | Ciclesonide Nasal Spray <sup>b)</sup> | -       | 3 (7 – 9)                         |
|       | Left         | No Treatment                          | -       |                                   |
| 4     | Right        | Ciclesonide Nasal Spray <sup>b)</sup> | +       | 3 (10 – 12)                       |
|       | Left         | No Treatment                          | +       |                                   |

<sup>a)</sup>: Ciclesonide Nasal Spray (Glucose-free, 100 mcg/Actuation)

<sup>b)</sup>: Ciclesonide Nasal Spray (Glucose-free, 25 mcg/Actuation)

The washing was conducted after 30 min of exposures.

The observation time was up to 72 hours (at 1, 24, 48 and 72 hours) for clinical signs, ophthalmology for anterior ocular segment and corneal epithelium.

Results: There were no drug related findings. The only finding was that one of three rabbits receiving ciclesonide at the 100 ug/actuation formulation without washing showed conjunctivae discharge at 1 hour post-dosing, but it disappeared by 24 hours postdosing. There was no remarkable finding in any other groups. Therefore, the current ciclesonide nasal spray formulations are considered to be non-irritating to rabbit eyes.

Study title: 28-day repeated nasal irritation study of hypotonic suspension preparation in rabbits (Study report 303E/99)

Background: There was only an upper limit ( $\leq 40$  mOsm) for the product osmolarity specified in the IND submission. The Division's review chemist recommended the sponsor to include (see Dr. Craig Bertha's review for the original submission dated 8/8/2002).

Summary of the study:

This non-GLP study investigated the irritability of a hypotonic suspension to nasal mucosa. Aqueous suspensions with osmotic pressures of 5 mOsm and 340 mOsm were prepared using water, cellulose/carboxycellulose sodium and benzalkonium chloride. New Zealand rabbits (3 males/group) were given the test suspensions in one nostril, 100 uL/dose, twice daily with a 6 hour interval for 28 days. The observations included clinical signs, necropsy and histopathology for particular local effects on nasal cavities. The results showed that the hypotonic suspension produced no irritation to rabbit nasal mucosa. Therefore, the intended clinical formulation with osmolarity of  $\leq 40$  mOsm would be unlikely to be irritating to the nasal mucosa.

#### 2.6.6.8 Special toxicology studies

No additional data submitted. In a study reviewed under [REDACTED] ciclesonide was negative in an anaphylaxis reaction assay as tested in active systemic anaphylaxis and passive cutaneous anaphylaxis in guinea pigs and in a mice-rats passive cutaneous anaphylaxis test.

#### 2.6.6.9 Discussion and Conclusions

The toxicities of ciclesonide as a result of systemic exposure have been reported and reviewed under [REDACTED] for the inhalation use of ciclesonide. The primary nonclinical concern for the current NDA 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 the current NDA, 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<sup>2</sup> 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<sup>2</sup> nasal surface area) for 4 weeks and 6 months. The NOAELs for the dog studies were 1200 mcg/day (5.5 mcg/cm<sup>2</sup> nasal surface area). On a mcg/cm<sup>2</sup> 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<sup>2</sup>).

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 glucocorticoid 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 C<sub>max</sub> values of 334 and 295 pg/mL for ciclesonide and des-ciclesonide, respectively; AUC<sub>0-24h</sub> 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:

Ciclesonide nasal spray is recommended for approval from a nonclinical standpoint, pending incorporation of recommended labeling revisions. The sponsor has established the nonclinical safety of intranasal use of ciclesonide nasal spray for the proposed clinical dose of up to 200 µg/day for [REDACTED]. It is, however, noted that the clinical review team currently does not consider there to be sufficient data to support the efficacy of the drug product below the age of 12.

The systemic toxicities of ciclesonide are well defined in the studies submitted under [REDACTED] for the inhalation treatment of asthma. For intranasal use of ciclesonide, a bridging toxicology program including 4-week studies in rats and dogs and a 6-month study in dogs was agreed upon and completed. In the 6-month dog study, local toxicities of nasal mucosal lymphoid atrophy were observed in dogs at the highest dose (4800 µg/day) and a NOAEL of 1200 µg/day (5.4 µg/cm<sup>2</sup>) was identified. This NOAEL provides a 4.3-fold margin of safety on a µg/cm<sup>2</sup> nasal surface area basis in comparison to the proposed human dosing (up to 200 µg/day, 1.25 µg/cm<sup>2</sup>). Systemic toxicities observed in the intranasal studies are similar to those observed in the previously conducted inhalation studies including body weight decrease, increases of blood triglyceride and cholesterol levels, adrenal suppression and lymphoid atrophy. At the highest dose in the 6-month dog study (4800 µg/day, systemic exposure level of AUC<sub>0-24h</sub> of 1161 pg.h/mL of RM-1 and 552 pg.h/mL of ciclesonide), testicular atrophy was observed in dogs. A NOAEL of 1200 µg/day was identified for systemic effects and this dose provides a 30-fold safety margin based on µg/kg body weight comparisons for the maximum proposed human dose of 200 µg/day.

Other noteworthy findings in the entire nonclinical program for ciclesonide are the following: positive results in an in vivo mouse micronucleus assay, teratogenic effects at doses of 5 ug/kg and above and embryocidal at 100 ug/kg and above in rabbits given by

subcutaneous route. Despite the positive genotoxicity finding, ciclesonide was negative in two 2-year carcinogenicity studies.

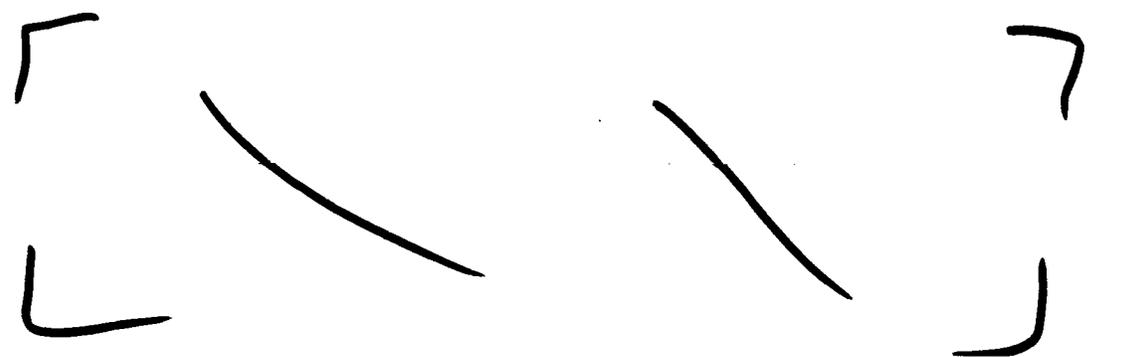
Unresolved toxicology issues:

There is no unresolved toxicology issue. The issue of testicular atrophy initially identified in the rat 4-week study has been resolved and is no longer considered to be treatment related (see the addendum to Review 2, dated 01/27/2003) The same finding identified in dogs occurs only at relatively high systemic exposures ( $AUC_{0-24h}$  of 1161 pg.h/mL of RM-1 and 552 pg.h/mL of Ciclesonide) which are not considered relevant for the proposed clinical use (human systemic exposures are expected to be negligible).

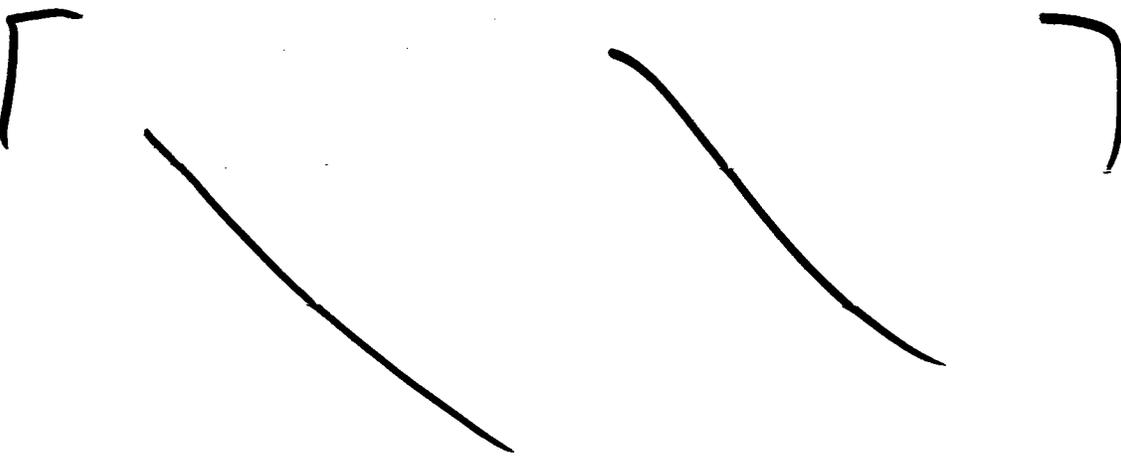
Recommendations:

This application is recommended for approval from the nonclinical perspective pending acceptance of recommended changes to the product label regarding the sections on Mechanism of Action, Carcinogenesis, Impairment of Fertility, Pregnancy, Nursing Mothers, and Overdosage.

Suggested labeling:



**CLINICAL PHARMACOLOGY**  
**Mechanism of Action**



2 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Inclusion of nonclinical lethal dose data provides physicians and consumers a better understanding of the acute overdose toxicity.

Signatures (optional):

Reviewer Signature \_\_\_\_\_

Supervisor Signature \_\_\_\_\_ Concurrence Yes \_\_\_ No \_\_\_

**APPENDIX/ATTACHMENTS**

1. Dose ratio calculation table:

| Drug:                              |       | <b>Ciclesonide<br/>nasal spray</b> |                     |                   |            |          |                |      |   |
|------------------------------------|-------|------------------------------------|---------------------|-------------------|------------|----------|----------------|------|---|
|                                    | age   | mg/dose                            | #<br>daily<br>doses | mg/day            | kg         | mg/kg    | factor         | n    |   |
| Pediatric dose                     |       |                                    |                     |                   |            |          |                |      |   |
| Adult dose                         | >12   | 0.05                               | 4                   | 0.2               | 50         | 0.00     | 37             |      |   |
|                                    |       |                                    |                     |                   | Dose Ratio |          | Rounded Dose F |      |   |
|                                    | route | mg/kg/day                          | factor              | mg/m <sup>2</sup> | Adults     | Children | Adults         | Chil |   |
| <u>Carcinogenicity:</u>            |       |                                    |                     |                   |            |          |                |      |   |
| rat                                | IH    | 0.193                              | 6                   | 1.158             | 7.82       |          | 8              |      |   |
| mouse                              | oral  | 0.9                                | 3                   | 2.7               | 18.24      |          | 20             |      |   |
| hamster                            |       |                                    | 4                   | 0                 | ---        | ---      | ---            |      |   |
| <u>Reproduction and Fertility:</u> |       |                                    |                     |                   |            |          |                |      |   |
| rat                                | oral  | 0.9                                | 6                   | 5.4               | 36.49      | N/A      | 35             |      | N |
| <u>Teratogenicity:</u>             |       |                                    |                     |                   |            |          |                |      |   |
| rabbit                             | SC    | 0.005                              | 12                  | 0.06              | 0.41       | N/A      | 1/2            |      | N |
| rat                                | oral  | 0.9                                | 6                   | 5.4               | 36.49      | N/A      | 35             |      | N |
| <u>Overdosage:</u>                 |       |                                    |                     |                   |            |          |                |      |   |
| mouse                              | ip    | 200                                | 3                   | 600               | 4054.05    |          | 4100           |      |   |
| rat                                | ip    | 200                                | 6                   | 1200              | 8108.11    |          | 8100           |      |   |
| mouse                              | oral  | 2000                               | 3                   | 6000              | #####      | #####    | 41000          |      |   |
| rat                                | oral  | 2000                               | 6                   | 12000             | #####      | #####    | 81000          |      |   |

2. IND 65,488 ORIGINAL REVIEW

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**HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS  
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

Original Review

**IND number:** 65488

**Serial No.** 000

**Date of submission:** 08/08/2002,

**Reviewer:** Huiqing Hao, Ph.D.

**Review Completion Date:** 09/30/02

**Communication to Sponsor:** Yes (X) No ( )

**Sponsor:** Teijin American, Inc.

**Drug:** TBN-15 (Ciclesonide nasal spray)

**Relevant INDs/NDAs/DMFs:** INL [REDACTED]

**Drug class:** Corticosteroid

**Indication:** Allergic rhinitis

**Route of administration:** Intranasally

**Clinical Formulation:** Composition includes: r-ciclesonide [REDACTED]  
cellulose [REDACTED]  
potassium sorbate [REDACTED] disodium edetate [REDACTED]  
hydrochloric acid [REDACTED] purified water: [REDACTED] Q.S  
to the designed volume).

**Proposed Clinical Protocol:** 14 days trial at doses of 25, 50, 100 or 200 µg/day in seasonal allergic rhinitis adults.

**Previous Clinical Experience:** Eight subjects (health or asymptomatic) was tested in study TBN-CL-001 ranged from 50 µg/day to 800 µg/day in Europe. Study data is not available yet.

**Previous reviews, date and reviewers:** None.

**Studies reviewed in this submission:**

1. Study on the effect of Ciclesonide in a guinea pig model of allergic rhinitis (Vol. 1.3, Study CN-P-01001)
2. 14-day intranasal toxicity study in male rats (Vol. 1.3, Study 0792/009)
3. 28-day intranasal toxicity study in rats (Vol. 1.4, Study 0792/017)
4. 14-day intranasal toxicity study in male dogs (Vol. 1.5, Study 0792/010)
5. 28-day intranasal toxicity study in dogs (Vol. 1.5, Study 0792/016)

**Studies not reviewed in this submission:** None

**Introduction:** Ciclesonide is current being developed in a metered dose inhaler for treatment of asthma (IND [REDACTED]). Sufficient systemic toxicity studies have been conducted by "inhalation route", the Division recommended intranasal bridging study for this IND.

## PHARMACOLOGY

### Study on the effect of Ciclesonide in a guinea pig model of allergic rhinitis

**Study No.** CN-P-01001

**Conducting Lab:** 

**GLP:** None.

**QA report:** No.

**Method:**

The guinea pig model of allergic rhinitis was prepared by systemical and local provocation with ovalbumin (OVA), an antigen. Severity of allergic rhinitis was measured by two end points: AUC<sub>(0-6h)</sub> of nasal respiratory resistance (NRR) and number of eosinophils in nasal lavage fluid.

Ciclesonide was administrated intranasally at a volume of 25 µg/nostril three times (49, 25 and 1 hour before antigen challenge). The doses of Ciclesonide tested were 0.1, 1, 10 µg/nostril. Budesonide 10 µg/nostril was used as positive control.

**Result:**

Dose-related decreases of nasal respiratory resistance and eosinophils in nasal lavage were as follows:

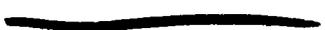
| Group                       | AUC <sub>(0-6h)</sub> of NRR (% of baseline.h) | Eosinophil number (x10 <sup>3</sup> ) |
|-----------------------------|------------------------------------------------|---------------------------------------|
| Saline                      | 622                                            | 0.209                                 |
| Control                     | 1658                                           | 3.625                                 |
| Ciclesonide (0.1µg/nostril) | 1046                                           | 1.426                                 |
| Ciclesonide (1µg/nostril)   | 743                                            | 0.513                                 |
| Ciclesonide (10 µg/nostril) | 694                                            | 0.326                                 |
| Budesonide (10 µg/nostril)  | 666                                            | 0.410                                 |

**Conclusion:** Ciclesonide had the similar efficacy as Budesonide in prevent allergic rhinitis in guinea pig model.

## TOXICOLOGY

### Ciclesonide nasal spray: 14-day nasal administration toxicity study in the rat

**Study No.** 0792/009

**Conducting Lab:** 

**GLP:** The study report was accompanied with a GLP statement.

**QA report:** Yes.

**Methods:** Crl:WI (WU) BR male rats were given intranasal instillation of Ciclosonide for 15 days. The group assignment was as follows:

| Formula type               | Group description | Drug conc. ( $\mu\text{g}/\mu\text{L}$ ) | Volume ( $\mu\text{L}/\text{nostril}$ ) | Dose ( $\mu\text{g}/\text{kg}$ ) | Animal numbers |           |
|----------------------------|-------------------|------------------------------------------|-----------------------------------------|----------------------------------|----------------|-----------|
|                            |                   |                                          |                                         |                                  | Main           | Satellite |
| Glucose free formula       | Control           | 0                                        | 15                                      | 0                                | 5              | -         |
|                            | Low dose          | 0.71                                     |                                         | 107                              | 5              | 5         |
|                            | High dose         | 2.86                                     |                                         | 429                              | 5              | 5         |
| Glucose containing formula | Control           | 0                                        |                                         | 0                                | 5              | -         |
|                            | Low dose          | 0.71                                     |                                         | 107                              | 5              | 5         |
|                            | High dose         | 2.86                                     |                                         | 429                              | 5              | 5         |

Satellite animals were used for toxicokinetics study.

**Observations:**

- Mortality: Twice daily.
- Clinical signs: Daily, before and after dosing 1, 2, and 4 hours.
- Body weights: Pre-study, and daily and before necropsy.
- Food consumption: Daily.
- Toxicokinetics: Blood samples were taken on day 1 and 14, at 0.5, 1, 2, 4, 6, and 24 hours after dosing.
- Hematology: Blood samples were collected from all animals in all animals treated with glucose-free formula on day 14 after an overnight fast.
- Urine analysis: In week 2.
- Clinical chemistry: On day 14, for all animals given glucose-free formula.
- Gross pathology: At sacrifice for all animals.
- Organ weights: For those listed in histopathology inventory (page 12) from all animals.
- Histopathology: Gross lesions of all animals were examined microscopically. Additionally, comprehensive examinations (histopathology inventory, page 12) were performed for animals of control and high dose group with glucose-free formula. The Low dose group with glucose-free formula and all animals given glucose-containing formula were examined locally (trachea, tracheal bifurcation, larynx, nasal turbinates and nasopharynx).

**Results:**

*Toxicokinetics:* The satellite animals were used for the TK study. The levels of M1 (B9207-021) were undetectable at the limit of quantification of 0.25ng/ml.

*Mortality:* None.

*Clinical signs:* None.

*Body weights:* The animals at 429 mg/kg (both in \_\_\_\_\_ formula) had 8% lower weight gain compared to the control.

*Food consumption:* Not apparently influenced.

*Hematology:* The examinations were performed for animals in \_\_\_\_\_ formula. No drug-related findings were seen.

*Clinical chemistry:* The examinations were performed for animals in glucose-free formula. Increases of sodium (HD, 3.5%), chloride (HD, 5.8%), urea (MD, 20%; HD, 48.9%), BUN (MD, 21%; HD, 50.4%), and ALT (LD 48%; HD, 29%), as well as decrease of phosphorus concentration (HD, 14%) were seen in drug-treated animals. None of these changes was considered toxicological significant.

*Urinalysis:* Animals at high dose (both glucose-free and glucose-containing formula) had 15.6% increase in both urine sodium and chloride.

*Organ weights:* Decreases of thymus weights (absolute and relative to body weight) were observed in drug-treated animals with glucose-free formula in a range of 13%-16% for LD and HD. There were no significant findings in animals with glucose-containing formula.

*Gross pathology:* No drug-related findings.

*Histopathology:* No drug-related findings.

**Conclusion:** There was no drug-related local toxicity in this study. Systemic toxicities were mild: decrease of body weight gain, changes on biochemical composition of the plasma and urine, decrease of thymus weights. The NOAEL was defined as 429 µg/kg.

**28-Day Nasal administration toxicity study in the rat with 28 day treatment-free period**

**Study No.** 0792/017 \_\_\_\_\_

**Conducting Lab.** \_\_\_\_\_

**GLP:** The study report was accompanied with a GLP statement.

**QA report:** Yes.

**Methods:** Wistar Crl:WI (WU) BR rats were given ciclesonide for 28 days plus drug-free for 28 days. The animal assignment was as following:

| Group           | Drug conc.<br>(µg/µL) | Dose volume<br>(µL/nostril) | Dose<br>(µg/kg) | Animals/sex/group |                |                 |
|-----------------|-----------------------|-----------------------------|-----------------|-------------------|----------------|-----------------|
|                 |                       |                             |                 | Main study        | Recovery group | Satellite study |
| Saline control  | 0                     | 15                          | 0               | 10                | -              | -               |
| Vehicle control | 0                     | 15                          | 0               | 10                | 6              | -               |
| Low dose        | 0.714                 | 15                          | 107             | 10                | -              | 5               |
| Mid dose        | 1.428                 | 15                          | 214             | 10                | -              | 5               |
| High dose       | 2.857                 | 15                          | 429             | 10                | 6              | 5               |

Satellite animals were used solely for toxicokinetic examinations.

All animals were observed for the follows:

- Mortality: Twice daily.
- Clinical signs: Daily.
- Body weights: Daily.
- Food consumption: Weekly.
- Ophthalmoscopy: Pre-treatment and in week 4.
- Toxicokinetics: Blood samples were taken from satellite animals on days 1 and 29 at 0.5, 1, 2, 4, 6, and 24 hours post-dose.
- Hematology: On day 28 after an overnight fast period.
- Clinical chemistry: The same blood samples of females as for hematology examinations were used. Males were not examined accidentally.
- Urine analysis: Samples were collected overnight from all animals in week 4. Food and water were removed during the collection.
- Organ weights: For those listed in the histopathology inventory on page 12.
- Histopathology: Gross lesions of all animals were examined microscopically. Additionally, comprehensive examinations (histopathology inventory, page 12) were performed for animals of control (both saline and vehicle control) and HD group. The LD and MD groups were examined locally (trachea, tracheal bifurcation, larynx, nasal turbinates and nasopharynx). Recovery animals were not examined.

#### Results:

*Toxicokinetics:* M1 (B9207-021) were undetectable at the limit of quantification of 0.25ng/ml.

*Mortality:* No drug-related deaths.

*Clinical signs:* No drug-related findings.

*Body weight gains:* Body weight gain decreases were observed by the end of week 4 (♂: HD, 12%; ♀: LD, 13%; MD, 8%; HD, 28%). The HD recovery males, but not females, showed 36% more body weight gained than control by the end of week 8.

*Food consumption:* No drug-related findings.

*Ophthalmology:* No drug-related findings.

*Hematology:* No toxicological significant changes. Increase of hemoglobin concentration and erythrocyte counts, decreases of mean cell volumes, shortening of prothrombin times and activated partial thromboplastin times were within  $\pm 5\%$  of control levels. Decreases of reticulocyte counts were reported in females (MD,  $\downarrow 15.6\%$ ; HD,  $\downarrow 20\%$ ). However, in repeat samples taken from the females at necropsy, most of the effects seen on Day 28 were not apparent. The only change of significance was an increase in reticulocyte counts (6.5, 15.9 and 20% in females at LD, MD and HD, respectively). This change probably was related to normal hemopoietic homeostasis following withdrawal of blood from the animals.

*Clinical chemistry:* No data from males were obtained. In females, triglyceride was increased 44, 49, and 58% at LD, MD, and HD respectively. This change was reversible as observed in 4-week recovery animals.

*Urinalysis:* No drug-related findings.

*Organ weights:* No drug-related findings.

*Gross pathology:* No remarkable findings.

*Histopathology:* No drug-related local toxicities were reported. Systemic toxicity was testis tubular atrophy. The incidence of the testicular findings is presented in the table below:

| Dose                         | C  | LD | MD | HD |
|------------------------------|----|----|----|----|
| N                            | 20 | 10 | 10 | 10 |
| Agonal congestion/hemorrhage | 1  | NE | NE | 0  |
| Tubular atrophy-unilateral   | 0  | NE | NE | 1  |
| Tubular atrophy-bilateral    | 0  | NE | NE | 3  |

Data of control group was from combined saline and vehicle group. NE: not examined.

**Conclusion:** Twenty-eight day intranasal treatment in rats with ciclosonide caused no local adverse effects. Based on local toxicity, the NOAEL was defined as 429  $\mu\text{g}/\text{kg}$ . Systemic toxicities included decrease body weights, elevation of triglyceride levels and tubular atrophy in testis. The testicular change was seen at the 429  $\mu\text{g}/\text{kg}$ . However, animals at lower doses were not examined. Based on systemic toxicity, particularly tubular atrophy, the NOAEL was not defined.

**Ciclesonide nasal spray: 14 day nasal administration toxicity study in the male dog****Study No.** 0792/010**Conducting Lab:** \_\_\_\_\_**GLP:** The study report was accompanied with a GLP statement.**QA report:** Yes.**Methods:** Male beagle dogs were given intranasal ciclesonide for 14 days. Each dog received 4 doses per day. Animal assignment was as follows:

| Test article                | Group description | Drug conc. (µg/µL) | Dose volume (µl/nostril) | Dose (µg/kg) | Male/g rroup |
|-----------------------------|-------------------|--------------------|--------------------------|--------------|--------------|
| Ciclesonide-GF*             | Control-GF        |                    | 840                      | 0            | 3            |
|                             | Low-GF            | 0.71               | 840                      | 120          | 3            |
|                             | High-GF           | 2.86               | 840                      | 480          | 3            |
| Ciclesonide-GC <sup>±</sup> | Low-GC            | 0.71               | 840                      | 120          | 3            |
|                             | High-GC           | 2.86               | 840                      | 480          | 3            |

**Observations:**

- Mortality: Twice daily.
- Clinical signs: Daily.
- Body weights: Pre-study, first day of dosing, weekly thereafter.
- Food consumption: Daily.
- Toxicokinetics: On day 1 and 14 at 0 hour after 2<sup>nd</sup> and last dose, and 0.5, 1, 2, 4, 6, 8, and 24 hrs after the last dose. Samples were analyzed for ciclesonide and its metabolites, B9207-021, using LC-MS/MS. The low limit of quantification (LLOQ) was 25 pg/ml for ciclesonide and B9207-021, using a 1 ml aliquot of serum.
- Hematology: In week 2, all animals treated with glucose-free formula.
- Clinical chemistry: The same blood samples as for hematology examinations were used.
- Urine analysis: Pre-treatment and in week 2 in animals of glucose-free control and high dose group.
- Organ weights: For those organs listed in histopathology inventory on page 12.
- Gross pathology: At necropsy.
- Histopathology: Only animals in glucose-free formula were examined. Tissues examined included: gross lesions of all animals, all tissues listed in the histopathology inventory (page 12) from the control and HD group, as well as thymus, trachea, larynx, epiglottis, soft palate, post-pharyngeal wall and nasal cavity from mid dose group.

**Results:**

**Toxicokinetics:** The drug exposure (C<sub>max</sub> and AUC) increased with the dose for each formulation (glucose-free and glucose-containing). Between day-1 and day-14, C<sub>max</sub>

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and AUC decreased in a range of 20-60% within each dose group, suggesting occurrence of enzyme induction. The table below presents the TK parameters of ciclesonide and its metabolites.

|                     | Dose<br>(µg/kg) | Ciclesonide  |       |                                     |       | B9207-021    |       |                                     |       |
|---------------------|-----------------|--------------|-------|-------------------------------------|-------|--------------|-------|-------------------------------------|-------|
|                     |                 | Cmax (pg/ml) |       | AUC <sub>(0-24h)</sub><br>(pg.h/ml) |       | Cmax (pg/ml) |       | AUC <sub>(0-24h)</sub><br>(pg.h/ml) |       |
|                     |                 | Day 1        | Day14 | Day 1                               | Day14 | Day 1        | Day14 | Day 1                               | Day14 |
| Ciclesonide-<br>GF* | 120             | 232          | 186   | 1300                                | 936   | 375          | 234   | 2240                                | 1363  |
|                     | 480             | 1520         | 535   | 6034                                | 3319  | 1601         | 866   | 10579                               | 6337  |
| Ciclesonide-<br>GC* | 120             | 282          | 214   | 680                                 | 378   | 402          | 271   | 1867                                | 788   |
|                     | 480             | NR           | 1054  | NR                                  | 3084  | 2900         | 1397  | 11966                               | 6714  |

\* glucose free formula, \* glucose containing formula. NR: no result. \* Where X= end of 4th dose.

*Mortality:* No deaths occurred.

*Clinical signs:* No signs of adverse reaction to treatment.

*Body weights:* No drug-related findings.

*Food consumption:* No significant changes.

*Hematology:* No drug-related findings.

*Clinical chemistry:* Increases of bilirubin (LD, 63%; HD, 100%) and cholesterol (LD, 40%; HD, 56%) were seen in drug-treated animals.

*Urinalysis:* No drug-related findings.

*Organ weights:* The changes of organ weights are given in the table below:

| Changes           | Control | LD | HD |
|-------------------|---------|----|----|
| ↑ Liver weights   | 0       | 10 | 25 |
| ↓ Thymus weights  | 0       | 23 | 60 |
| ↓ Adrenal weights | 0       | 4  | 16 |

*Gross pathology:* No remarkable findings.

*Histopathology:* There were no local findings attributable to the drug treatment. Systemic finding was typical for corticosteroid: minimal-grade thymic atrophy in 3/3 animals at HD. There were no findings associated with the liver weight increases.

**Conclusion:** Intranasal administration of Ciclesonide up to 480 µg/kg for 14 days caused no local toxicities in male dogs. Systemic toxicities were decreases of thymic and adrenal weights, increase cholesterol levels, and thymic atrophies. The NOAELs were

defined as 480 µg/kg based on local toxicity and 120 µg/kg based on systemic toxicity, particularly thymic atrophy.

**Ciclesonide nasal spray: 28-day nasal administration toxicity study in the dog with a 28 days treatment-free period**

**Study No.** 0792/016

**Conducting Lab:** ~~XXXXXXXXXXXXXXXXXXXX~~

**GLP:** The study report was accompanied with a GLP statement.

**QA report:** Yes.

**Methods:** Beagle dogs were given Ciclesonide intranasally 4 doses/day for 28 days and allowed to recover for 28 days. The experimental design was as follows:

| Group     | Drug concentration (µg/µL) | Dose volume (µl/nostril) | Dose (µg/kg) | Animal number |   |          |   |
|-----------|----------------------------|--------------------------|--------------|---------------|---|----------|---|
|           |                            |                          |              | Main study    |   | recovery |   |
|           |                            |                          |              | ♂             | ♀ | ♂        | ♀ |
| Saline    | 0                          | 840                      | 0            | 3             | 3 |          |   |
| Vehicle   | 0                          | 840                      | 0            | 3             | 3 | 2        | 2 |
| Low dose  | 0.714                      | 840                      | 120          | 3             | 3 |          |   |
| Mid dose  | 1.428                      | 840                      | 240          | 3             | 3 |          |   |
| High dose | 2.857                      | 840                      | 480          | 3             | 3 | 2        | 2 |

**Observations:**

- Mortality: Twice daily.
- Clinical signs: Daily.
- Body weights: Weekly.
- Food consumption: Daily.
- Ophthalmoscopy: Pre-treatment and at the end of week 4.
- ECG: Pre-treatment and at the end of week 4.
- Toxicokinetics: Blood samples were collected pre-dose, on day 1 and 27 immediately after the 2<sup>nd</sup> and last dose, as well as 0.5, 1, 2, 4, 6, 8, and 24 hours after the last dose.
- Hematology: Blood samples were withdrawn in week 4 (all animals) and week 8 (treatment-free animals).
- Clinical chemistry: The same blood samples as for hematology examinations were used.
- Urine analysis: Overnight urine was collected from all animals pre-treatment and in week 4.
- Organ weights: Organ weights were obtained from these listed in the histopathology inventory (page 12).
- Gross pathology: At necropsy.
- Histopathology: Gross lesions in all animals were examined microscopically. Control (saline and vehicle group) and HD group were examined comprehensively (inventory on page 12). The animals at LD, MD and recovery groups were examined locally (thymus adrenal, trachea, tracheal bifurcation, epiglottis, soft palate, post-pharyngeal wall and nasal cavity).

**Results:**

**Toxicokinetics:** AUC increased with dose. Generally this was equal to or greater than the increase in dose. Drug exposures decreased between Day 1 and Day 27 (AUC, ↓ 20-65%; C<sub>max</sub>, ↓ 20-75%) except AUC for females at HD, suggesting enzyme induction occurred similarly to the observation in the 14-day study (0792/010). Males had higher AUC than females. The table below presents the TK parameters for M1 (B9207-021).

| Dose (µg/kg) | Males                    |        |                                  |        | Females                  |        |                                  |        |
|--------------|--------------------------|--------|----------------------------------|--------|--------------------------|--------|----------------------------------|--------|
|              | C <sub>max</sub> (pg/ml) |        | AUC <sub>(x-24h)</sub> (pg.h/ml) |        | C <sub>max</sub> (pg/ml) |        | AUC <sub>(x-24h)</sub> (pg.h/ml) |        |
|              | Day 1                    | Day 27 | Day 1                            | Day 27 | Day 1                    | Day 27 | Day 1                            | Day 27 |
| 120          | 364                      | 92     | 637                              | 197    | 170                      | 126    | 575                              | 399    |
| 240          | 223                      | 361    | 1249                             | 965    | 168                      | 130    | 800                              | 399    |
| 480          | 666                      | 505    | 3153                             | 2513   | 545                      | 333    | 2078                             | 2300   |

\* where x = end of 4<sup>th</sup> dose. The animal numbers were 3/sex/dose at LD and MD, and 4/sex at HD.

**Mortality and clinical signs:** There were no deaths or clinical signs of adverse reaction to treatment.

**Body weights gains:** Decreases of body weight gains were observed in treated groups by the end of week-4 (♂: LD, 48%; MD, 0%; HD, 74%. ♀: LD, 43%; MD, 98%; HD, 102%). These changes were reversible as seen in recovery animals.

**Food consumption:** No drug-related findings.

**Ophthalmology:** No drug-related findings.

**ECG:** No drug-related findings.

**Hematology:** No drug-related findings.

**Clinical chemistry:** Cholesterol and triglyceride levels were higher in drug treated animals (see details in the following table)

|                    | ♂ |    |    |    | ♀ |    |    |    |
|--------------------|---|----|----|----|---|----|----|----|
|                    | C | LD | MD | HD | C | LD | MD | HD |
| ↑ Cholesterol (%)  | 0 | 0  | 15 | 24 | 0 | 16 | 3  | 26 |
| ↑ Triglyceride (%) | 0 | 22 | 51 | 65 | 0 | 66 | 2  | 47 |

**Organ weights:** Ciclesonide caused decreases of thymic weights and adrenal weights. Also, it caused a mild increase of liver weights. The table below presents the details of these organ weight changes.

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|                       | ♂ |    |    |    | ♀  |    |    |    |
|-----------------------|---|----|----|----|----|----|----|----|
|                       | C | LD | MD | HD | C  | LD | MD | HD |
| ↑ Liver weights (%)   | 0 | 0  | 13 | 11 | 0  | 23 | 10 | 8  |
| ↓ Thymus weights (%)  | 0 | 0  | 51 | 43 | 44 | 0  | 16 | 30 |
| ↓ Adrenal weights (%) | 0 | 22 | 8  | 23 | 0  | 0  | 13 | 20 |

Gross pathology: No drug-related findings.

Histopathology: Local findings were atrophy of lymphoid aggregates associated with mucosa of the maxilloturbinate and nasal pharyngeal regions or nasal cavity. Systemic toxicities were adrenal cortex atrophy and thymic atrophy. The similar local findings, but not systemic findings, were observed in the recovery animals. The following table presents the details described above.

#### Histopathology incidence or index

|                                  |                                  | ♂   |     |     |     | ♀   |     |     |     |
|----------------------------------|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|
|                                  |                                  | C   | LD  | MD  | HD  | C   | LD  | MD  | HD  |
| 4-wk treatment                   | Adrenal cortex atrophy incidence | 0/6 | 0/3 | 0/3 | 1/3 | 0/6 | 0/3 | 0/3 | 0/3 |
|                                  | Thymic atrophy incidence         | 0/6 | 0/3 | 2/3 | 2/3 | 0/6 | 0/3 | 0/3 | 2/3 |
|                                  | Lymphoid atrophy index           | 6.8 | 5   | 3   | 3.5 | 6   | 6.5 | 3.5 | 4.5 |
| 4-wk treatment<br>+4 wk recovery | Adrenal cortex atrophy incidence | 0/2 |     |     | 0/2 | 0/2 |     |     | 0/2 |
|                                  | Thymic atrophy incidence         | 0/2 |     |     | 0/2 | 0/2 |     |     | 0/2 |
|                                  | Lymphoid atrophy index*          | 5   |     |     | 3   | 2.5 |     |     | 2.5 |

\* maxilloturbinate region and nasopharyngeal region were examined for the size of lymphoid aggregates. The data presented in the table were mean value of these two sites. Index: sum of product of incidence x size (grade) at the particular dose level. Lymphoid aggregates were graded into 4 levels. Grade 0=lymphoid aggregate not present, grade 3=medium to large aggregate + prominent germinal center. Aggregate sizes for Grader 1 and 2 were in between grade 0 and 3.

**Conclusion:** Intranasal administration of Ciclesonide to dogs caused both local and systemic adverse effects: decreases of body weight gains, increases of cholesterol and triglyceride levels, and atrophies of thymus, adrenal cortex, and lymphoid aggregates in the nasal mucosa. Atrophies of thymus and lymphoid aggregate occurred at doses of 240 µg/kg and above, and adrenal atrophy occurred at dose of 480 µg/kg.

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Histopathology inventory for IND 65.488

| Study                   | 0792/009   | 0792/017   | 0792/010   | 0792/016   |
|-------------------------|------------|------------|------------|------------|
| Species (duration)      | Rat 14-day | Rat 28-day | Dog 14-day | Dog 28-day |
| Adrenals                | X*         | X*         | X*         | X*         |
| Aorta                   |            | X          |            | X          |
| Bone Marrow smear       | X          | X          | X          | X          |
| Bone (femur)            | X          | X          | X          | X          |
| Brain                   | *          | X*         | *          | X*         |
| Cecum                   |            | X          |            | X          |
| Cervix                  |            |            |            |            |
| Colon                   |            | X          |            | X          |
| Duodenum                |            | X          |            | X          |
| Epididymis              |            | X          |            | X          |
| Epiglottis              |            |            | X          | X          |
| Esophagus               | X          | X          | X          | X          |
| Eye                     |            | X          |            | X          |
| Fallopian tube          |            |            |            |            |
| Gall bladder            |            |            |            |            |
| Gross lesions           | X          | x          | X          | X          |
| Harderian gland         |            |            |            |            |
| Heart                   | *          | X*         | *          | X*         |
| Ileum                   |            | X          |            | X          |
| Injection site          |            |            |            |            |
| Jejunum                 |            | X          |            | X          |
| Kidneys                 | X*         | X*         | X*         | X*         |
| Lachrymal gland         |            |            |            |            |
| Larynx                  | X          | X          | X          | X          |
| Liver                   | X*         | X*         | X*         | X*         |
| Lungs                   | X          | X*         | X          | X*         |
| Lymph nodes, bronchial  |            | X          |            | X          |
| Lymph nodes mandibular  | X          | X          | X          | X          |
| Lymph nodes, mesenteric | X          | X          | X          | X          |
| Mammary Gland           | X          | X          | X          | X          |
| Nasal cavity            | X          | X          | X          | X          |
| Nasal turbinates        | X          | X          |            |            |
| Nasal pharynx           | X          | X          |            |            |
| Optic nerves            |            | X          |            | X          |
| Ovaries                 |            | X*         |            | X*         |
| Pancreas                |            | X          |            | X          |
| Parathyroid             |            | X          |            | X          |
| Peripheral nerve        |            |            |            |            |
| Pituitary               | *          | x*         | *          | X*         |
| Post-pharyngeal wall    |            |            | X          | X          |
| Prostate                | X*         | x*         | X*         | X*         |
| Rectum                  |            | X          |            | X          |
| Salivary gland          |            | X*         |            | X*         |
| Sciatic nerve           |            | X          |            | X          |
| Seminal vesicles        | X          | X*         |            |            |
| Skeletal muscle         |            |            |            |            |

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|                      |    |    |    |    |
|----------------------|----|----|----|----|
| Skin                 | X  | X  | X  | X  |
| Soft palate          |    |    | X  | X  |
| Spinal cord          |    | X  |    | X  |
| Spleen               | X* | X* | X* | X* |
| Sternum              | X  | X  | X  | X  |
| Stomach              | X  | X  |    | X  |
| Testes               | X* | X  | X* | X  |
| Thymus               | X* | X* | X* | X* |
| Thyroid              | X* | X* | X* | X* |
| Tongue               |    | X  |    | X  |
| Trachea              | X  | X  | X  | X  |
| Tracheal bifurcation | X  | X  | X  | X  |
| Urinary bladder      | X  | X  |    | X  |
| Uterus               |    | X* |    | X* |
| Vagina               |    | X  |    | X  |
| Zymbal gland         |    |    |    |    |

X, histopathology performed; \*, organ weight obtained.

### Summary and Evaluation

In guinea pig model, intranasal administration of Ciclesonide was as effective as Budesonide in preventing allergic rhinitis.

There were four toxicity studies in the current submission, all by intranasal administration: the 14-day in male rats, 14-day in male dogs, 28-day in rats, and 28-day in dogs. Drug-related local toxicity was observed only in 28-day dog study as atrophy of lymphoid aggregate in nasal mucosa at doses of 240 µg/kg and above. Systemic toxicities in both species were decrease of body weight gain, increases of triglyceride and/or cholesterol levels, atrophy of thymus and adrenal cortex with associated decreased weights of these organs. These systemic findings were generally dose and treatment duration related. In addition to these typical findings for glucocorticoid, tubular atrophy in testis was seen in the 28-day rat study. Based on local toxicity the NOALEs were defined as 429 µg/kg in the 14- and 28-day rat studies, 480 µg/kg in the 14-day dog study, and 120 µg/kg in the 28-day dog study. Based on the systemic toxicity, NOAELs were 429 in the 14-day rat study, not defined in the 28-day rat study, 120 µg/kg in the 14- and 28-day dog studies.

The following table presents the safety margins as comparing the proposed human dose (200µg/day or 4 µg/kg body weight, or 1.25 µg/cm<sup>2</sup> NESA for 14 days) with each of the animal NOAEL. NOAELs were convert to µg per cm<sup>2</sup> of nasal epithelial surface area when local toxicity is the only concern.

|                   | Animal study    | NOAEL                           | Human dose                      | Safety margin |
|-------------------|-----------------|---------------------------------|---------------------------------|---------------|
| Local toxicity    | 14 days in rats | 7.7 µg/cm <sup>2</sup><br>NESA  | 1.25 µg/cm <sup>2</sup><br>NESA | 6.2           |
|                   | 14 days in dogs | 21.8 µg/cm <sup>2</sup><br>NESA |                                 | 17.5          |
|                   | 28 days in rats | 7.7 µg/cm <sup>2</sup><br>NESA  |                                 | 6.2           |
|                   | 28 days in dogs | 5.45 µg/cm <sup>2</sup><br>NESA |                                 | 4.36          |
|                   |                 |                                 |                                 |               |
| Systemic toxicity | 14 days in rats | 429 µg/kg                       | 4µg/kg                          | 107           |
|                   | 14 days in dogs | 120 µg/kg                       |                                 | 30            |
|                   | 28 days in rats | Not defined                     |                                 | -             |
|                   | 28 days in dogs | 120 µg/kg                       |                                 | 30            |

Therefore, the proposed clinical trial for 14 days is safe to proceed. The NOAEL was not established in 28-day study in rats due to the finding in testis and it should be addressed for clinical trial longer than 14 days.

Additionally, local lymphoid atrophy observed in dogs was considered a typical finding with corticosteroids treatment and less toxicological significant than the findings of testicular atrophy seen in rats. Therefore, the rat was identified as an appropriate species for the 6-month bridging study.

It was noticed that the AUC (as well as Cmax) values of B9207-021 were significantly different in the 14-day dog study and 28-day dog study. The sponsor needs to provide explanation for these discrepancies.

**Recommendation:**

The proposed dose up to 200µg/day for 14 days is safe to proceed.

There was no NOAEL defined in rat 28-day study due to the findings of testicular atrophy. This issue needs to be addressed for clinical trial longer than 14 days. Additionally, rats instead of dogs are recommended for the 6-month bridging study. The discrepancies reported on the Cmax and AUC values of B9207-021 in the 14-day dog study and 28-day dog study need to be explained. All of these should be conveyed to the sponsor.

**Draft letter to the sponsor:**

Your submission of IND 65.488, dated 08/08/2002 has been reviewed. We have the following comments:

1. It was noticed that tubular atrophy in testis occurred in rats given 429µg/kg Ciclesonide for 28 days (study number 0792/017). The incidence was not examined

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- in rats given lower doses. Therefore, no NOAEL was defined in this study. We recommend this issue be addressed for clinical trials longer than 14 days.
2. As the result of this testicular toxicity finding, rat rather than dog appears to be the appropriate species for the proposed 6-month bridging study.
  3. Explain the significant differences in  $C_{max}$  and AUC values of B9207-021 reported in the 14-day dog study (study # 0792/010) and 28-day dog study (study # 0972/016).

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Huiqing Hao, Ph.D., Pharmacologist

3. IND 65,488 REVIEW 2

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       § 552(b)(4) Draft Labeling

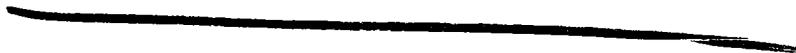
       § 552(b)(5) Deliberative Process



**Recommendation:**

There are insufficient data to support the sponsor's assertion that the testicular atrophy in the rat 28-day study is unrelated to TBN-15 treatment. Sponsor should be requested to provide historical control data to clarify this issue.

As this issue is unresolved, the NOAEL remains undefined in the 4-week rat study. Clinical trials longer than 2 weeks are not supported. Rat rather than dog remains to be the recommended species for the 6-month bridging study.



**Draft letter to the sponsor:**

Your submission for IND 65,448, dated Dec. 10, 2002 has been reviewed.

We consider the data you provided are insufficient to support your statement that the observed testicular atrophy observed in the Study 0792/017 is not likely to be related to treatment with TBN-15. Historical control data of such finding from your laboratory may be helpful to clarify this issue.

As this issue is unresolved, the Division's recommendations remain the same as stated in the letter dated Nov. 4, 2002. No NOAEL was defined in rat 4-week study and this needs to be addressed for clinical trials longer than 14 days. Rat rather than dog is the recommended species for the 6-month bridging study.

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Huiqing Hao, Ph. D., Pharmacologist

4. IND 65,488 ADDENDUM TO REVIEW 2

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this page is the manifestation of the electronic signature.**  
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/s/

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Huiqing Hao  
4/7/03 12:15:24 PM  
PHARMACOLOGIST

Joseph Sun  
4/7/03 02:45:25 PM  
PHARMACOLOGIST  
I concur.

5. IND65,488 REVIEW 4

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IND65488  
Page 1 of 7**HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS  
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION****Review 4****IND number:** 65488**Serial No.** N-14, N-38, N-039**Date of submission:** 12/16/2003, 10/14/2004, 10/21/2004**Review Completion Date:** 11/23/2004**Addendum reviewer:** Huiqing Hao, Ph. D.**Communication to Sponsor:** Yes ( ) No (X)**Sponsor:** Teijin American, Inc.**Drug:** TBN-15 (Ciclesonide nasal spray)**Relevant INDs/NDAs/DMFs:** [REDACTED]**Drug class:** Corticosteroid**Indication:** Allergic rhinitis**Route of administration:** Intranasally**Clinical formulation:** Ciclesonide 25-100 ug/70 µL aqueous suspension containing

microcrystalline cellulose [REDACTED] hydroxymethylcellulose [REDACTED]

[REDACTED] potassium sorbate [REDACTED] disodium edetate [REDACTED]

[REDACTED] hydrochloric acid [REDACTED] (appropriate amount) and purified  
water (Q.S to the designed volume)**Proposed Clinical Protocol:** clinical trial in patient 12 years and older with perennial allergic rhinitis using ciclesonide nasal spray (200 ug/day, 100 ug/nostriil/day) for 52 weeks (N-039, 10/22/2004)**Background:**

Preclinical studies for ciclesonide have been conducted for inhalation administration in a MDI formulation. For the current IND (intranasal administration), a 6-month intranasal bridging study in an appropriate species for chronic intranasal use in humans is required and this message has been conveyed to the sponsor during the pre-IND meeting (2/22/2002). The sponsor provided an interim report and final report of the 6-month dog bridging study on 12/16/2003 (N-14) and 10/14/2004 (N-38), respectively.

On 12/12/2003, the sponsor Submitted a clinical trial protocol to use ciclesonide nasal spray (200 ug/day, 100 ug/nostriil/day) for 48 weeks in patient 12 years and older with perennial allergic rhinitis (serial number 013). In the current submission (N-039, 10/21/04), the sponsor proposed to extend the clinical trail to 52 weeks. Additionally, the sponsor proposed a single dose (200 ug) trial in seasonal allergic rhinitis patients 18 years and older using Environment Exposure Chamber (EEC) to assess the onset of action of ciclesonide.

**Studies reviewed:**

26-Week intranasal bridging study in dogs

**A 26-week intranasal toxicity study of Ciclesonide Nasal Spray in beagles followed by a 12-week recovery period**

**Key study findings:**

Toxicities observed in dogs given ciclesonide nasal spray for 6 months included slight decreases in leukocyte and lymphocyte counts, adrenal suppression, thymus atrophy, atrophy of mucosal-associated lymphoid tissue of nasal cavity, as well as increased incidence/severity of testicular atrophy, vacuolation and mononuclear cell infiltrations. NOAEL was defined as 1200 ug/day as that all the toxicity findings were seen in the HD of 4800 ug/day.

**Study No.** ~~24-50~~

**Conducting Lab:** ~~\_\_\_\_\_~~

**Study initiation and completion date:** Initiated on 08/22/2002 and completed on 01/30/2004

**GLP:** Yes (with no signature page included)

**QA report:** No QA report attached

**Methods:** Beagle dogs (age of 9-11 months, body weights ranged 9.6-15 kg for males and 8.8-15 kg for females) were given ciclesonide nasal spray daily for 6 months and the study design was as the following

| Test article  | Dose (ug/day) | Concentration (ug/70 uL) | Volume (uL/day) | Dose (ug/cm <sup>2</sup> nasal surface) | Animals M/F |
|---------------|---------------|--------------------------|-----------------|-----------------------------------------|-------------|
| Normal Saline | 0             | 0                        | 1680            | 0                                       | 6/6*        |
| vehicle       | 0             | 0                        | 1680            | 0                                       | 6/6*        |
| ciclesonide   | 300           | 25                       | 840             | 1.36                                    | 4/4         |
| ciclesonide   | 1200          | 100                      | 840             | 5.44                                    | 4/4         |
| ciclesonide   | 4800          | 200                      | 1680            | 21.75                                   | 6/6*        |

- \*2 animals per sex for recovery (12 weeks)
- Vehicle formulation was the same as the ciclesonide nasal spray (contained microcrystalline cellulose, hydroxymethylcellulose, potassium sorbate, disodium edetate, hydrochloric acid and purified water) but with no ciclesonide.
- The test article was administered into both nasal cavities with 3 sprays for each session. Two controls (saline and vehicle) and HD animals received 4 sessions per day, LD and MD animals received 2 sessions per day.
- Dog nasal cavity surface area of 220.7 cm<sup>2</sup> was used in the calculations of dose/cm<sup>2</sup> nasal surface.
- Note: dose volume of 70 uL per actuation (ex-valve volume) was used as the dose volume reached the dog nostrils. In the human study proposed in the submission N-013 on 12/12/2003 the dose volume of 50 uL out of 70 uL was considered actual volume reached the human nostrils.

**Observations:**

- Clinical signs: Control and HD, 6 times daily; LD and MD 4 times daily.

- Body weights: Pre-study, weekly during dosing, and at necropsy.
- Food consumption: Daily.
- ECG: Once during acclimation, once at each of Week 12 and 25 of dosing and once at Week 12 of recovery.
- Ophthalmology: Once during acclimation, once at each of Week 12 and 25 of dosing and once at Week 12 of recovery.
- Hematology: Blood samples were collected from all animals, once during acclimation, once at Week 13 and 26 of dosing and once at Week 12 of recovery.
- Serum biochemistry: Once during acclimation, once at Week 13 and 26 of dosing and once at Week 12 of recovery.
- Urinalysis: Once during acclimation, once at Week 13 and 26 of dosing and once at Week 12 of recovery.
- Toxicokinetics: Blood samples were taken on day 1, Week 13 and 26 before administration, immediately after the final session of administration (forth session: controls and HD; second session: LD and MD), and 0.5, 1, 2, 4, 6, 8 and 24 hours after the final administration.
- Gross pathology: At sacrifice for all animals.
- Organ weights: For those listed in histopathology inventory from all animals.
- Histopathology: a comprehensive list of tissues from all animals (histopathology inventory) were examined.

**Results:**

*Clinical signs:* Salivation was observed in the drug treated and vehicle groups throughout the 6-month, and the saline control dogs in the first 2 months. During the recovery period, no abnormalities were noted. Sporadic vomiting and soft stool were observed in drug treated, vehicle and saline treated dogs. None of these clinical signs were considered drug related.

*Body weights:* No drug-related findings.

*Food consumption:* No drug-related findings.

*ECG:* No drug-related findings.

*Ophthalmology:* No drug-related findings

*Hematology:* The dose related decreases of WBC were observed during the treatment period as listed in the table below. No similar changes were seen in recovery dogs.

|                   | Males   |         | Females |         |
|-------------------|---------|---------|---------|---------|
|                   | Week 13 | Week 26 | Week 13 | Week 26 |
| Δ % saline group  | ↓12-25% | ↓10-28% | ↓10-14% | ↓6-20%  |
| Δ % vehicle group | ↓10%    | ↓10-19% | ↓15-22% | ↓22-34% |

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Compared to the concurrent controls (saline and vehicle), a decrease in eosinophils count in HD males (51-57%) was observed at Week 13 but not in Week 26. No similar change was seen in corresponding females. This finding was not considered toxicological significant.

*Serum biochemistry:* No drug-related findings.

*Urinalysis:* No drug-related findings

*Toxicokinetics:* Drug exposures (C<sub>max</sub> and AUC) in general were proportional to the doses and there were no significant dose accumulation over 26 weeks of dosing. There were no gender related differences noted.

Pharmacokinetic parameters in the beagle 26-week intranasal study

| Dose<br>(ug/body)                                     | Day 0                   |                             |                                   | Week 13                 |                             |                                   | Week 26                 |                             |                                   |
|-------------------------------------------------------|-------------------------|-----------------------------|-----------------------------------|-------------------------|-----------------------------|-----------------------------------|-------------------------|-----------------------------|-----------------------------------|
|                                                       | T <sub>max</sub><br>(h) | C <sub>max</sub><br>(pg/mL) | AUC <sub>0-24h</sub><br>(pg.h/mL) | T <sub>max</sub><br>(h) | C <sub>max</sub><br>(pg/mL) | AUC <sub>0-24h</sub><br>(pg.h/mL) | T <sub>max</sub><br>(h) | C <sub>max</sub><br>(pg/mL) | AUC <sub>0-24h</sub><br>(pg.h/mL) |
| Ciclesonide (B9207-015) in male beagles               |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 0.5                     | 185                         | 259                               | 2.8                     | 203                         | 736                               | 1.2                     | 163                         | 268                               |
| 1200                                                  | 0.8                     | 192                         | 324                               | 0.9                     | 391                         | 588                               | 0.7                     | 274                         | 525                               |
| 4800                                                  | 0.8                     | 930                         | 1703                              | 0.4                     | 875                         | 3357                              | 0.7                     | 1044                        | 2574                              |
| Ciclesonide (B9207-015) in female beagles             |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 1.3                     | 233                         | 527                               | 1.0                     | 112                         | 278                               | 0.8                     | 166                         | 198                               |
| 1200                                                  | 0.9                     | 441                         | 641                               | 1.3                     | 306                         | 536                               | 1.1                     | 367                         | 698                               |
| 4800                                                  | 0.6                     | 648                         | 1360                              | 1.2                     | 1017                        | 3068                              | 1.2                     | 988                         | 2375                              |
| Ciclesonide metabolite (B-9207-021) in male beagles   |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 1.4                     | 145                         | 302                               | 1.0                     | 169                         | 484                               | 1.5                     | 136                         | 436                               |
| 1200                                                  | 1.8                     | 184                         | 827                               | 1.8                     | 333                         | 1549                              | 1.5                     | 218                         | 1011                              |
| 4800                                                  | 0.9                     | 1012                        | 4519                              | 1.3                     | 1082                        | 6744                              | 1.1                     | 1131                        | 5970                              |
| Ciclesonide metabolite (B-9207-021) in female beagles |                         |                             |                                   |                         |                             |                                   |                         |                             |                                   |
| 300                                                   | 1.5                     | 102                         | 289                               | 1.5                     | 113                         | 273                               | 1.3                     | 164                         | 332                               |
| 1200                                                  | 0.9                     | 298                         | 1005                              | 1.3                     | 270                         | 1152                              | 1.4                     | 361                         | 1423                              |
| 4800                                                  | 0.8                     | 722                         | 3517                              | 1.3                     | 1128                        | 5440                              | 1.2                     | 1204                        | 5591                              |

*Gross pathology:* No drug-related findings.

**Organ weights:** the HD dogs were observed with decreased adrenal and thymus weights compared to the saline and vehicle groups (adrenal: males, ↓ 40%; females, ↓40-45%; thymus: males, ↓7-10%; females, ↓41-44%).

**Histopathology:** The pharmacological effects related findings including adrenal cortical atrophy, thymus atrophy, decreased the number of tracheal epithelial goblet cells, and atrophy of mucosa-associated lymphoid tissue in the respiratory mucosa of the nasal cavity were seen in the HD dogs. Additionally, focal seminiferous tubule atrophy was seen in the HD and vehicle dogs, vacuolation and mononuclear cell infiltrations in the testes were seen in the HD dogs only. There were no similar testicular findings in the

saline control group. Therefore, the testicular findings were considered treatment related. The LD and MD were observed with slightly more severe thymic atrophy than saline and vehicle controls. The recovery dogs (previously at HD) showed seminiferous tubule atrophy (1/2) only and all other findings appeared reversed to normal. No abnormal findings were seen in the saline and vehicle control recovery dogs. The following table presents the details of histopathological incidences.

|                                 | saline               | vehicle              | LD                   | MD                   | HD                     |
|---------------------------------|----------------------|----------------------|----------------------|----------------------|------------------------|
| N                               | 4/sex/dose           |                      |                      |                      |                        |
| Adrenal cortical atrophy        |                      |                      |                      |                      | M, 4(1)<br>F, 4(1)     |
| Thymic atrophy                  | M, 4(1.3)<br>F, 2(1) | M, 3(1.4)<br>F, 2(1) | M, 4(1.7)<br>F, 2(2) | M, 3(1.7)<br>F, 2(2) | M, 4(2.8)<br>F, 3(1.7) |
| ↓Tracheal goblet cells          |                      |                      |                      |                      | M, 3(1.3)<br>F, 1(1)   |
| NALT atrophy                    |                      |                      |                      |                      | M, 2(1)<br>F, 2(1)     |
| Left testis:                    |                      |                      |                      |                      |                        |
| Seminiferous tubule atrophy     |                      | 1(1)                 |                      |                      | 1(2)                   |
| Seminiferous tubule vacuolation |                      |                      |                      |                      | 1(1)                   |
| Mononuclear cell infiltration   |                      |                      |                      |                      | 2(1)                   |
| right testis:                   |                      |                      |                      |                      |                        |
| Seminiferous tubule atrophy     |                      | 1(1)                 |                      |                      | 2(1.5)                 |
| Seminiferous tubule vacuolation |                      |                      |                      |                      | 1(1)                   |
| Mononuclear cell infiltration   |                      |                      |                      |                      | 2(1)                   |

NALT: nasal associated lymphoid tissues; The numbers in the ( ) represent grade of the changes as 1=very slight, 2=slight, 3=moderate, 4=marked; The blanks indicate zero incidences.

**Conclusion and discussion:** Toxicities observed in dogs given ciclesonide nasal spray for 6 months included slight decreases in leukocyte and lymphocyte counts, adrenal suppression, thymus atrophy, atrophy of mucosal-associated lymphoid tissue of nasal cavity, as well as increased incidence/severity of testicular atrophy, vacuolation and mononuclear cell infiltrations. Compared to the 12-month inhalation study in dogs, the systemic exposures (AUC) in the current study seemed higher (50-60 X). The testicular findings reported in the current intranasal study, but not in the previous 12-month inhalation study, may be the reflective of the toxicity of the higher exposure. The sponsor considered the testicular findings not drug-related as that were seen in the vehicle control dogs in the current study and they were previously reported spontaneous findings in dogs in a publication. However, data from a published paper could not be used as a representative of the historical control of the study conducting laboratory. Furthermore, absence of such findings in saline control dogs in the current study and increased incidence/severity in the HD dogs do not support the sponsor's argument.

The sponsor's concluded the NOALE of 4800 ug/dog/day (HD). However, based on the histopathological findings of lymphoid atrophy and testicular changes, the NOAEL should be 1200 ug/dog/day (MD). This NOAEL provided sufficient safety margins for the proposed clinical doses up to 200 ug/day (4.3-fold on a mg/cm<sup>2</sup> nasal surface area basis and 30-fold on a mg/kg basis). Therefore, the current proposal of intranasal dose of 200 ug for 52 weeks is acceptable.

## Histopathology inventory for IND 65,488

|                         |          |  |  |  |
|-------------------------|----------|--|--|--|
| Study                   | SBL24-50 |  |  |  |
| Species                 | dog      |  |  |  |
| Adrenals                | X        |  |  |  |
| Aorta                   | X        |  |  |  |
| Bone Marrow smear       | X        |  |  |  |
| Bone (femur)            | X        |  |  |  |
| Brain                   | X        |  |  |  |
| Cecum                   | X        |  |  |  |
| Cervix                  | X        |  |  |  |
| Colon                   | X        |  |  |  |
| Duodenum                | X        |  |  |  |
| Epididymis              | X        |  |  |  |
| Esophagus               | X        |  |  |  |
| Eye                     | X        |  |  |  |
| Fallopian tube          |          |  |  |  |
| Gall bladder            | X        |  |  |  |
| Gross lesions           | X        |  |  |  |
| Harderian gland         | X        |  |  |  |
| Heart                   | X        |  |  |  |
| Ileum                   | X        |  |  |  |
| Injection site          |          |  |  |  |
| Jejunum                 | X        |  |  |  |
| Kidneys                 | X        |  |  |  |
| Lachrymal gland         |          |  |  |  |
| Larynx                  | X        |  |  |  |
| Liver                   | X        |  |  |  |
| Lungs                   | X        |  |  |  |
| Lymph nodes, cervical   | X        |  |  |  |
| Lymph nodes mandibular  | X        |  |  |  |
| Lymph nodes, mesenteric | X        |  |  |  |
| Mammary Gland           | X        |  |  |  |
| Nasal cavity            | X        |  |  |  |
| Optic nerves            |          |  |  |  |
| Ovaries                 | X        |  |  |  |
| Pancreas                | X        |  |  |  |
| Parathyroid             | X        |  |  |  |

|                  |   |  |  |  |
|------------------|---|--|--|--|
| Peripheral nerve | X |  |  |  |
| Pharynx          |   |  |  |  |
| Pituitary        | X |  |  |  |
| Prostate         | X |  |  |  |
| Rectum           | X |  |  |  |
| Salivary gland   |   |  |  |  |
| Sciatic nerve    |   |  |  |  |
| Seminal vesicles | X |  |  |  |
| Skeletal muscle  | X |  |  |  |
| Skin             | X |  |  |  |
| Spinal cord      | X |  |  |  |
| Spleen           | X |  |  |  |
| Sternum          |   |  |  |  |
| Stomach          | X |  |  |  |
| Testes           | X |  |  |  |
| Thymus           | X |  |  |  |
| Thyroid          | X |  |  |  |
| Tongue           | X |  |  |  |
| Trachea          | X |  |  |  |
| Urinary bladder  |   |  |  |  |
| Uterus           | X |  |  |  |
| Vagina           | X |  |  |  |
| Zymbal gland     |   |  |  |  |

X, histopathology performed  
\*, organ weight obtained

**Recommendation:**

The clinical proposal of intranasal administrations of ciclesonide at 200 ng for 52 weeks is acceptable.

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Huiqing Hao, Ph.D., Pharmacologist

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/s/

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I concur.

6. IND 65,488 REVIEW 7

**2.6 PHARMACOLOGY/TOXICOLOGY REVIEW**

**2.6.1 INTRODUCTION AND DRUG HISTORY**

**IND number:** 65,488

**Review number:** 7

**Sequence number/date/type of submission:** N-075, 10/25/2005, IT

**Information to sponsor:** Yes ( ) No (X)

**Sponsor and/or agent:** Altana

**Manufacturer for drug substance:** \_\_\_\_\_

**Reviewer name:** Huiqing Hao, Ph.D.

**Division name:** Pulmonary and Allergy Products

**Review completion date:** 06/20/2006

**Drug:**

Trade name: None

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<sub>32</sub>H<sub>44</sub>O<sub>7</sub>, 540.7

**Relevant INDs/NDAs/DMFs:** IND 65,488, \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Drug class:** Glucocorticoid steroid

**Intended clinical population:** Seasonal and perennial allergic rhinitis in adults and children 2 years of age and older.

**Route of administration:** Nasal spray

**Proposed clinical protocol:** None

**Previous clinical experience:** An NDA for Ciclesonide MDI treatment of asthma has been submitted \_\_\_\_\_ Clinical trials in adults up to 1 year at 200 ug/day by intranasal administration have been completed under the current IND.

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

**Studies reviewed within this submission:**

1. Effect of ciclesonide on IL-8 production by human nasal epithelial cells (29/2005)
2. Effect of ciclesonide on IL-8 production by human bronchial epithelial cells (prolonged efficacy) (30/2005)
3. Investigation of possible synergistic actions of ciclesonide with anti-histamine on monocyte function in vitro (151/2005)
4. Study of metabolism of ciclesonide in the human nasal epithelia cells (3/2005)
5. Measurement of concentration of cicleonide and its metabolites in rabbit nasal mucosa after intranasal administration of TBN-15 (4/2005)

**Studies not reviewed within this submission:**



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## 2.6.2 PHARMACOLOGY

### 2.6.2.2 Primary pharmacodynamics

Mechanism of action: No studies were submitted.

Drug activity related to proposed indication:

1. Effect of ciclesonide on IL-8 production by human nasal epithelial cells: Primary cultured human nasal epithelial cells were treated with various steroids for 1 hour prior to IL-1 $\beta$  stimulation (2 ug/mL, 24 hours). The concentration of IL-8 in the culture medium was measured by ELISA. The potency of the inhibition on IL-8 release from human nasal epithelial cells was in an order of mometasone furoate > fluticasone propionate > ciclesonide > budesonide > beclomethasone. The maximum degree of inhibition was similar among all of the compounds (33-38%).

EC50 values and maximum inhibition of IL-8 release from human nasal epi. cells

|                             | EC50 value (nM) | Maximum inhibition |
|-----------------------------|-----------------|--------------------|
| Ciclesonide                 | 0.81            | 35.82%             |
| Beclomethasone Dipropionate | 22.0            | 33.81%             |
| Budesonide                  | 4.70            | 36.07%             |
| Fluticasone propionate      | 0.123           | 34.28%             |
| Mometasone furoate          | 0.0257          | 37.81%             |

2. Effect of ciclesonide on IL-8 production by human bronchial epithelial cells (prolonged efficacy): Primary cultured human bronchial epithelial cells were exposed to various steroids for 1 hour prior to IL-1 $\beta$  stimulation (2 ug/mL, 24 hours). The steroid treatment included three different settings: continuous treatment-the cells were exposed to steroids throughout the study; temporary treatment-the cells were washed with steroid free medium after 1 hour of steroid exposure; washing treatment-the cells were washed and incubated for 30 min with steroid free medium. The results showed the order of potency of inhibition on IL-8 production as continuous > temporary > washing setting (see the table below). Upper and lower values were obtained from two different experiments.

EC50 value of steroid inhibition on IL-8 production in different exposure setting

|                        | EC50 (nM)  |           |         |
|------------------------|------------|-----------|---------|
|                        | continuous | temporary | washing |
| Ciclesonide            | 1.15       | 3.05      | 3.14    |
|                        | 0.46       | 1.61      | 2.88    |
| Budesonide             | 0.44       | 16.3      | 66.1    |
|                        | 0.41       | 18.1      | 28.7    |
| Fluticasone propionate | 0.051      | 0.18      | 0.54    |
|                        | 0.049      | 0.23      | 0.48    |

With continuous treatment, Ciclesonide potency was similar to that of Budesonide, but was about 10fold less potent than that of Fluticasone. Comparing the EC50 values across the different types of exposures, it appeared that washout caused significant reduction of drug potency for Budesonide and Fluticasone but not Ciclesonide, suggesting that Ciclesonide has a prolonged efficacy.

- Investigation of possible synergistic actions of Ciclesonide with anti-histamines on monocyte function in vitro: Monocytes from human peripheral blood were incubated with test compounds followed by stimulation with LPS (1  $\mu$ M, 24 hours). Afterwards, cytokines (TNF $\alpha$ , IL-6, MCP-1 and RANTES) in the culture medium were determined by ELISA. The results showed that Azelastine (antihistamine) up to 10  $\mu$ M did not affect the LPS induced cytokine release from monocytes. Ciclesonide and its active metabolite M1 inhibited LPS-induced production of TNF $\alpha$ , IL-6, MCP-1 and RANTES. Combination of ciclesonide or M1 with Azelastine showed a trend of synergistic effects of inhibition on cytokine release.

|               | IC50 value (nM) |                        |     |               |
|---------------|-----------------|------------------------|-----|---------------|
|               | Ciclesonide     | Ciclesonide+Azelastine | M1  | M1+Azelastine |
| TNF- $\alpha$ | 749             | 224                    | 51  | 59            |
| IL-6          | 1494            | 908                    | 64  | 79            |
| MCP-1         | 531             | 237                    | 74  | 85            |
| RANTES        | 1069            | 612                    | 168 | 170           |

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

### 2.6.4.5 Metabolism

- Study of metabolism of ciclesonide in the human nasal epithelial cells: Primary cultured human nasal epithelial cells (HNEC) were exposed to ciclesonide for 1 hour and followed by washout of test drug and incubation for an additional 0.5-24 hours. It was confirmed that the metabolites B9207-021 and M4 (fatty acid conjugates of B9207-021) were generated. The amount of ciclesonide decreased with time, while B9207-021 levels remained stable over time from 0.5 to 24 hour. On the other hand, conjugates of B9207-021 with oleic acid and palmitic acid increased with time ; predominantly, the oleic acid conjugate of B9207-021 was produced (BYK204147). The following table presents the levels each of compound over the observation period of 24 hours.

| Compound            | N of samples | Amount (pmol/dish) |       |       |       |
|---------------------|--------------|--------------------|-------|-------|-------|
|                     |              | 0.5 h              | 3 h   | 6 h   | 24 h  |
| Ciclesonide         | 5            | 28.82              | 5.12  | 2.50  | 0.31  |
| B9207-021           | 5            | 6.08               | 5.76  | 7.34  | 5.39  |
| B9207-021/oleate    | 5            | 17.13              | 21.59 | 32.58 | 48.43 |
| B9207-021/palmitate | 5            | 0.48               | 0.71  | 1.30  | 1.87  |

2. Measurement of concentration of ciclesonide and its metabolites in rabbit nasal mucosa after intranasal administration of TBN-15: rabbits were given a single dose of ciclesonide nasal spray (143 ug/animal, 1 actuation/nostril, both nostrils). At designated time points (0.5-24 hours postdosing), the nasal cavity was washed and nasal mucosa was collected and analyzed for the concentrations of ciclesonide, B9207-021, and M4 (oleic acid and palmitic acid conjugates of B9207-021). The results indicated that ciclesonide was activated in the nasal mucosa of rabbits as B9207-021 and M4 metabolites were generated (50-168 pmol/g tissue for oleate conjugate and 1-3 pmol/g tissue for palmitate conjugate). B9207-021 in the nasal mucosa attained the maximum concentration (415 pmol/g tissue) at 0.5 h after administration and decreased with time. B9207-021 was confirmed to be present in the nasal mucosa even at 24 hour after administration (45.5 pmol/g tissue). The table below presents the details for the levels of each compound over the 24 hours of observation time.

| Compound            | Animal N | Concentration (pmol/g tissue) |       |       |       |      |
|---------------------|----------|-------------------------------|-------|-------|-------|------|
|                     |          | 0.5 h                         | 8 h   | 12 h  | 16 h  | 24 h |
| Ciclesonide         | 5        | 2737.3                        | 508.1 | 411.2 | 422.2 | 67.7 |
| B9207-021           | 5        | 415.0                         | 262.5 | 166.5 | 170.3 | 45.5 |
| B9207-021/oleate    | 5        | 81.6                          | 167.5 | 107.1 | 102.2 | 50.3 |
| B9207-021/palmitate | 5        | 1.0                           | 3.0   | 1.5   | 3.1   | 1.3  |

## OVERALL CONCLUSION AND RECOMMENDATIONS

### Summary:

The current submission included three in vitro pharmacology studies and two metabolism studies. The results of the studies are summarized below and they do not have a significant impact on the overall development of the program.

### Pharmacology:

In primary cultures of human nasal epithelial cells, ciclesonide inhibited IL-8 production induced by IL-1 $\beta$  with an EC<sub>50</sub> that was within the range of other steroids. This inhibition was prolonged although it decreased after removal of the drug. Ciclesonide inhibited cytokine (TNF- $\alpha$ , IL-6, MXP-1 and RANTES) release from human monocytes, and showed a trend of a synergistic effect when administered in combination with azelastine (an antihistamine drug), although azelastine alone had no such effect.

Metabolism:

In primary cultured human nasal epithelial cells, ciclesonide was metabolized to the active metabolite B9207-021 which was further conjugated with oleic acid and palmitic acid. Similarly, a ciclesonide nasal spray in rabbits resulted in generation of B9207-021 and its fatty acid conjugates (oleic acid and palmitic acid) in nasal mucosa. B9207-21 and its conjugates with oleate and pamitate have been identified in previous studies using human and rat lung slices. The fatty acid conjugate is reversible and therefore is considered as a reservoir for active drug

Internal comments:

None

External comments (to sponsor):

None.

Signatures (optional):

Reviewer Signature     Huiqing Hao, Ph.D.    

Supervisor Signature     Timothy McGovern     Concurrency Yes       
No

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5 Page(s) Withheld

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