

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-658

PHARMACOLOGY REVIEW(S)



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: **21-658**
SERIAL NUMBER: **000**
DATE RECEIVED BY CENTER: **7/10/2007**
PRODUCT: **Alvesco (Ciclesonide MDI)**
INTENDED CLINICAL POPULATION: **Asthma patients**
SPONSOR: **Nycomed**
DOCUMENTS REVIEWED: **E-submission, labeling**
REVIEW DIVISION: **Pulmonary and Allergy Products**
PHARM/TOX REVIEWER: **Huiqing Hao, Ph.D.**
PHARM/TOX SUPERVISOR: **Timothy McGovern, Ph.D.**
DIVISION DIRECTOR: **Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER: **Colette Jackson**

Date of review submission to DFS: 12/20/2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This drug is recommended to be approved from a pharmacology and toxicology perspective.

B. Recommendation for nonclinical studies

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

C. Recommendations on labeling

Modified language is recommended for the information pertaining to the sections on "Use in Specific Populations: Pregnancy", "Overdosage", "Mechanism of Action", and "Carcinogenesis, Mutagenesis, Impairment of Fertility".

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

All relevant nonclinical studies were reviewed in the original NDA review or supporting IND reviews. Animals receiving repeat dose ciclesonide inhalation (up to 6 months in rats and 12 months in dogs) showed typical glucocorticoid effects in a dose- and duration-dependent manner. These effects were decreases of body weights (or body weight gains), adrenal suppression, and lymphoid tissue atrophy (thymus, spleen and lymph nodes, bronchus-associated lymphoid tissue).

Ciclesonide was negative in the Ames test, CHO/HGPRT forward mutation assay, chromosome aberration assay in human lymphocyte, and micronucleus test in V79 cells, but positive in an in vivo micronucleus test in mice.

Two-year carcinogenicity studies in mice and rats demonstrated that this drug did not induce any tumor incidences.

Ciclesonide did not produce any reproductive toxicities to fertility and early embryonic development, embryofetal development, or prenatal and postnatal development in rats. However, subcutaneous administration to rabbits demonstrated that this drug was teratogenic and embryocidal.

B. Pharmacologic activity

Pharmacological effects of ciclesonide are primarily exerted by its de-esterified metabolite which had 120-fold higher binding affinity to glucocorticoid receptors than ciclesonide. The drug exhibited immunosuppressive properties in several in vitro models [inhibition of Concanavalin A-stimulated rat spleen cell proliferation, inhibition of Anti-CD3-induced cytokine synthesis in mouse Th2 lymphocytes; inhibition of IL-2 production by CD3-stimulated human peripheral blood mononuclear cells (PBMCs), and inhibition of Concanavalin A-induced Proliferation of PBMCs]. This drug also inhibited mouse ear inflammation

induced by croton oil and rat granuloma formation induced by subcutaneously implanted cotton pellets. In a rat ex vivo model, ciclesonide inhibited bradykinin-induced mucosal leakage in trachea. Intratracheal administration of ciclesonide reduced cell and protein accumulation in BAL in ovalbumin sensitized rats and inhibited sephadex-induced lung edema in rats. Additionally, ciclesonide reduced airway hyper-responsiveness induced by an allergen as measured by the response to methacholine.

R-Ciclesonide has _____ s than S-Ciclesonide, thus **b(4)**
RCiclesonide was developed.

C. Nonclinical safety issues relevant to clinical use
There are no nonclinical safety issues.

APPEARS THIS WAY ON ORIGINAL

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-658

Review number: 2

Sequence number/date/type of submission: 000/July 10, 2007/AZ
000/October 31, 2007/BL

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Sanofi-Aventis U.S. LLC

Manufacturer for drug substance: _____ b(4)

Reviewer name: Huiqing Hao, Ph.D.

Division name: Pulmonary and Allergy Products

Review completion date: 12/20/07

Drug:

Trade name: Alvesco

Generic name: Ciclesonide

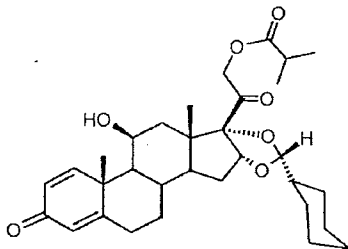
Code name: Byk Gulden B9207-015

Chemical name: [11β, 16α]-16, 17-[Cyclohexylmethylend) bis(oxy)-11-hydroxy-21-(2-methyl-1-oxypropoxy)pregna-1, 4-diene-3, 20- dione

CAS registry number: 141845-82-1

Molecular formula/molecular weight: C₃₂H₄₄O₇, 540.7

Structure:



b(4)

Relevant INDs/NDAs/DMFs: IND 65,488 (intranasal), IND 53,391 (inhalation) and NDA 22-004 (nasal administration, 12 yrs and older); NDA 22-124 (nasal administration 6-11 years old); DMF of _____ DMFs: 1 _____

Drug class: Glucocorticoid steroid

Intended clinical population: Maintenance treatment of asthma as prophylactic therapy in adult _____ patients _____ years of age and older. Of note, the clinical

b(4)

recommendation will be for approval in ages 12 and above. The recommended maximum clinical dose will be — mcg/day.

b(4)

Clinical formulation: Solution formulation of Ciclesonide with ' _____
a — USP and ' _____ HFA-134a (1,1,1,2-tetrafluoroethane) propellant.

Route of administration: Oral Inhalation (MDI)

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

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The original submission of this NDA dated 12/22/2003 was reviewed and recommended for approval from a non-clinical perspective (see review of 9/30/2004). There were no unresolved non-clinical issues. However, the Division concluded that the application was “approvable” due to clinical efficacy and CMC issues (10/21/2004 letter). The current resubmission provided additional data to address the deficiencies and the medical review team indicates that clinical data support use up to 640 mcg/day in subjects 12 years and older. This review evaluates the nonclinical sections of the proposed product label.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues.

Recommendations:

This NDA is recommended for approval from the nonclinical perspective pending acceptance of recommended changes to the product label regarding the sections on “Use in Specific Populations: Pregnancy”, “Overdosage”, “Mechanism of Action”, and “Carcinogenesis, Mutagenesis, Impairment of Fertility”.

Suggested labeling:

The sponsor submitted proposed product labeling in the original NDA submission and updated the label in the current resubmission (7/10/2007). The relevant nonclinical sections of the label are reviewed below with suggested inserts noted by underlining and suggested deletions noted by strikethroughs with a rationale for the edits provided. It should be noted that the current label review is based on the determination by the clinical review team that there is insufficient data to support the efficacy of the drug product in subjects below the age of 12. Should sufficient data be provided in the future, appropriate text regarding the exposure ratios between animals and children should be

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 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

APPENDIX/ATTACHMENTS

Calculated animal to human exposure ratios based on mg/m² comparisons.

Drug:		ALVESCO						
age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m ²	
Adult	>12	0.32	2	0.64	50	0.0128	37	0.4736
		conv. factor	mg/m ²	Dose Ratio		Rounded Dose Ratio		
route	mg/kg/d			Adults	Children	Adults	Children	
Carcinogenicity:								
rat	ih	0.193	6	1.158	2.4451	N/A	2	N/A
mouse	po	0.9	3	2.7	5.701	N/A	6	N/A
Repro/Fertility:								
rat	po	0.9	6	5.4	11.402	N/A	10	N/A
Teratogenicity:								
rabbit	sc	0.005	12	0.06	0.1267	N/A	< 1	N/A
rat	po	0.9	6	5.4	11.402	N/A	10	N/A
Overdosage:								
mouse	po	2000	3	6000	12669	N/A	13000	N/A
mouse	ip	200	3	600	1266.9	N/A	1300	N/A
rat	po	2000	6	12000	25338	N/A	25000	N/A
rat	ip	200	6	1200	2533.8	N/A	2500	N/A

Conversion, Correction, and Rounding Factors:

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

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/s/

Huiqing Hao
12/20/2007 01:14:32 PM
PHARMACOLOGIST

Timothy McGovern
12/20/2007 01:29:12 PM
PHARMACOLOGIST
I concur.

HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

Chemistry Consult (Impurity Qualification)

NDA number: 21658

Date of submission: 10/30/2003

Request Date: 07/20/2004

Sponsor: Aventis

Reviewer: Huiqing Hao, Ph.D.

Division: Division of Pulmonary and Allergy Drug Products

HFD: 570

Review Completion Date: 08/30/04

Drug: Ciclesonide MDI

Drug Class: Glucocorticoid

Indication: Asthma

Route of administration: Oral Inhalation (MDI)

Chemist Who Requested the Consult: Arthur Shaw, Ph.D.

Description of the Consult

This is a request to evaluate the toxicology study for qualifying the _____
_____ impurity at the proposed acceptance criteria level of _____. The 3-
month dog study using _____ spiked formulation was submitted in the current NDA.

b(4)

Toxicity of R-ciclesonide spiked with _____% _____ in beagle dogs as dry powder aerosol inhalation for 3 months

Research report #: 131/2003

Study /protocol #: HD0859

Volume #: 2.6.7.17

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

this study because of the typical histopathological findings. However, there were no new toxicities observed in this study compared to the studies with no spiking of _____ Toxicity potency of _____-spiked R-ciclesonide was not higher than that without spiking as shown in the following table (Dogs in Study 273/98 were given R-ciclesonide without spiking for 3 months). In conclusion, there are no toxicity differences between the _____ spiked formulation and that without the spiking.

b(4)

	Study 131/2003 (current)				Study 273/98 (previous)			
	94		180		106		222	
Delivered dose of ciclesonide (µg/kg)	94		180		106		222	
M1*	10.46		23.57		5.2		16	
AUC _{0-24h} (µg.h/ml)	10.46		23.57		5.2		16	
	♂	♀	♂	♀	♂	♀	♂	♀
Adrenal atrophy	1/4	0/4	4/4	2/4	3/4	4/4	4/4	4/4
Spleen atrophy	3/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4

*AUCs of M1 rather than ciclesonide are available to compare these two studies. The AUC of M1 in Study 131/2003 was generated by R-M1 and -M1 and in Study 273/98 was generated by R-M1 only; The doses of 94 and 180 µg/kg in the current study were LD and MD; the doses of 106 and 222 µg/kg in the study 273/98 were MD and HD, respectively.

The human maximum daily dose of _____ based on proposed specification of _____ is _____. The pulmonary deposited doses of this study were 4.8, 9, and 14 µg/kg which provide safety margins of 16, 30 and 46, respectively. Thus, the specification of _____ in R-ciclesonide is qualified.

Recommendation:

The proposed impurity acceptance criteria of _____ in R-ciclesonide product is acceptable.

Huiqing Hao, Ph.D., Pharmacologist

Histopathology inventory

Study	131/2003			
Species (duration)	Dog 3 months			
Adrenals	X			
Aorta	X			
Bone Marrow smear	X			
Bone (femur)				
Brain	X*			
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis	X*			
Esophagus	X			
Eye	X			
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart	X*			
Ileum				
Injection site				
Jejunum	X			
Kidneys	X*			
Lachrymal gland				
Larynx				
Liver	X*			
Lungs	X*			
Lymph nodes, bronchial	X			
Lymph nodes submandibular	X			
Lymph nodes, mesenteric	X			
Mammary Gland	X			
Nasal cavity	X			
Optic nerves				
Ovaries	X*			
Pancreas	X*			
Parathyroid				
Peripheral nerve				
Pharynx				

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

X, histopathology performed; *, organ weight obtained.

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

/s/

Huiqing Hao
8/30/04 04:40:11 PM
PHARMACOLOGIST

Joseph Sun
9/1/04 12:11:56 PM
PHARMACOLOGIST
I concur.



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: 21-658
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 12/22/03
PRODUCT: Alvesco™ (Ciclesonide inhalation aerosol)
INTENDED CLINICAL POPULATION: Asthmatic patients
SPONSOR: Aventis, Inc.
DOCUMENTS REVIEWED: Electronic NDA, Module 4
REVIEW DIVISION: Division of Pulmonary and Allergy Drug Products
(HFD-570)
PHARM/TOX REVIEWER: Huiqing Hao, Ph.D.
PHARM/TOX SUPERVISOR: Joe Sun, Ph.D.
DIVISION DIRECTOR: Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER: Colette Jackson

Date of review submission to Division File System (DFS): Sep. 30, 2004

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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, mutagenesis, impairment of fertility, pregnancy, nursing mothers, and overdose.

II. Summary of nonclinical findings

A. brief overview of nonclinical findings

Animals receiving repeat dose ciclesonide inhalation (up to 6 months in rats and 12 months in dogs) showed typical glucocorticoid effects in a dose and treatment duration dependent manner. These effects were decreases of body weights (or body weight gains), adrenal suppression, and lymphoid tissue atrophy (thymus, spleen and lymph nodes, bronchus-associated lymphoid tissue).

Ciclesonide was tested negative in Ames test, CHO/HGPRT forward mutation assay, chromosome aberration assay in human lymphocyte, and micronucleus test in V79 cells, but positive in an in vivo micronucleus test in mice.

Two -Year carcinogenicity studies in mice and rats demonstrated that this drug did not induce any tumor incidences.

In reproductive toxicity aspect as tested in rats, ciclesonide did not have toxicities to fertility and early embryonic development, embryofetal development, or prenatal and postnatal development. However, subcutaneous administration to rabbits demonstrated that this drug was teratogenic and was embryocidal.

B. Pharmacologic activity

Pharmacological effects of ciclesonide are primarily exerted by its de-esterified metabolite which had 120-fold higher binding affinity to glucocorticoid receptor than ciclesonide. The drug exhibited immunosuppressive properties in several in vitro models [inhibition of Concanavalin A-stimulated rat spleen cell proliferation, inhibition of Anti-CD3-induced cytokine synthesis in mouse Th2 lymphocytes; inhibition of IL-2

Production by CD3-Stimulated human peripheral blood mononuclear cells (PBMCs); Inhibition of Con A-induced Proliferation of PBMCs]. This drug also inhibited mouse ear inflammation induced by croton oil and rat granuloma formation induced by subcutaneously implanted cotton pellets. In rat ex vivo model, ciclesonide inhibited bradykinin-induced mucosal leakage in trachea. Intratracheal administration of ciclesonide reduced cell and protein accumulation in BAL in ovalbumin sensitized rats and inhibited sephadex-induced lung edema in rats. Additionally, ciclesonide reduced airway hyper-responsiveness induced by allergen as measured by the response to methacholine.

R-Ciclesonide has _____ S-Ciclesonide, thus R-Ciclesonide was developed.

b(4)

C. Nonclinical safety issues relevant to clinical use
There are no nonclinical safety issues.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21,658

Review number: 1

Sequence number/date/type of submission: 000/Dec. 22, 2003/original

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Aventis Inc.

Manufacturer for drug substance: _____

b(4)

Reviewer name: Huiqing Hao

Division name: Pulmonary and Allergy Drug Products

HFD #: 570

Review completion date: 09/30/2004

Drug:

Trade name: Alvesco Inhalation Aerosol 11 mcg, 80 mcg, 160 mcg

Generic name: Ciclesonide Inhalation Aerosol

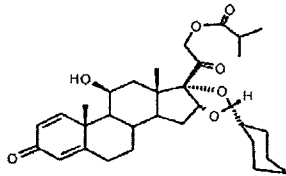
Code name: Byk Gulden B9207-015

Chemical name: [11 β , 16 α]-16, 17-[Cyclohexylmethylidene] bis(oxy)-11-hydroxy-21-(2-methyl-1-oxypropoxy)pregna-1, 4-diene-3, 20-dione

CAS registry number: 141845-82-1

Molecular formula/molecular weight: C₃₂H₄₄O₇, 540.7

Structure:



Relevant INDs/NDAs/DMFs: IND53391 and DMF _____

Drug class: Glucocorticoid Steroid

Intended clinical population: Mild to moderate asthmatic patients age of _____ years or older

b(4)

Clinical formulation: Solution formulation of Ciclesonide with _____, USP and _____% w/w HFA-134a (1,1,1,2-tetrafluoroethane) propellant.

Composition of each strengths of ciclesonide inhalers are listed in the following table.

Ingredient	Ex-actuation dose (µg/actuation)	Quantity			Function
		% w/w	gram per filled canister*		
			60 actuation	120 actuation	
ciclesonide	80	_____			corticosteroid
	160	_____			
Dehydrated alcohol, USP	80	_____			
	160	_____			
HFA-134a	80	_____			propellant
	160	_____			

b(4)

*based on a target fill weight of 6.1 g or — g respectively for the 60 and 120 actuation products.

Route of administration: Inhalation (MDI)

Recommended dose: Highest recommended dose are — µg BID in adults and 160 µg — in children — years old.

b(4)

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

Studies reviewed within this submission:

Preclinical Studies Submitted and Reviewed in this NDA:

Study	Location in Model 4 (study #)
Pharmacology:	
Receptor binding studies to determine the affinity of R-Ciclesonide, R-M1 and Fluticasone for the estrogen, progesterone, and testosterone receptors	2001/1531
Binding affinities of BYK199393 and BYK204147 (ciclesonide metabolites of the M4 family) in the glucocorticoid receptor binding assay	237/2001
Characterization of BYK20432-a report on the action of BYK20432 through the glucocorticoid and progesterone receptors	204/2001
Inhibition of concanavalin A-stimulated rat spleen cells by ciclesonide, its R- and S- epimer and their metabolites, and by budesonide	89/94
Inhibition of anti-CD3/CD28 mAb-stimulated human CD4+ T-cell functions by B9207-015 concanavalin	61/2001
Effect of B9207-015 on lipopolysaccharide-induced tumor necrosis	271/2000

factor-alpha release in human whole blood Effect of B9207-015 on lipopolysaccharide-induced tumor necrosis factor-alpha release in human monocytes and monocyte-derived dendritic cells	274/2000
Effects of intratracheally administered Ciclesonide, its Metabolite R-M1 and Budesonide on cell and protein accumulation in 48h-bronchalveolar lavage fluid of ovalbumin-sensitized/challenged Brown-Norway rats	49/2001
Effects of single intratracheal administration of B9299-011 on cell accumulation and protein concentration in BAL of ovalbumin-sensitized Brown-Norway rats	72/96
Attenuation of bradykinin-induced mucosal leakage in rat trachea by topical budesonide	193/94
Study on the effect of inhaled Ciclesonide in a rat model of allergen sensitized and induced airway hypersensitiveness	128/2001
Study on the effect of inhaled ciclesonide in a rat model of asthma	129/2001
Comparison of the antiproliferative activity of the metabolite of ciclesonide (the "R-epimer") and of the metabolite of the s-epimer of ciclesonide in the rat (cotton pellet granuloma test)	123/2001
Mineralocorticoid and glucocorticoid activity of orally administered ciclesonide, budesonide, metabolite I, epimer R and epimer S in the rat (28 days)	82E/94
Effects of intratracheally administered ciclesonide, its metabolite R-M1 and budesonide on cell and protein accumulation in 48h-bronchoalveolar lavage fluid of ovalbumin/challenged Brown-Norway rats	49/2001
Reduction of croton oil-induced mouse ear edema by budesonide	87/94
Antiproliferative activity of budesonide after local administration in the rat (cotton pellet granuloma test)	77/94
Safety Pharmacology: 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
Pharmacokinetics: Pharmacokinetic, radiokinetic, and ¹⁴ C excretion/mass balance study of ciclesonide in male B6C3F1 mice	DMPK/USA /2003/0031
Pharmacokinetic, radiokinetic, and ¹⁴ C excretion/mass balance study of ciclesonide in male Wistar rats	DMPK/USA /2003/0032
Pharmacokinetic, radiokinetic, and ¹⁴ C excretion/mass balance study of ciclesonide in female Himalayan rabbits	DMPK/USA /2003/0030
Pharmacokinetic, radiokinetic, and ¹⁴ C excretion/mass balance study of ciclesonide in male Beagle dogs	DMPK/USA /2003/0033
Comparison of pharmacokinetics and pharmacodynamics (suppression of cortisol) in dogs following intravenous injection of B9207-021 itself or	239/98

b(4)

ad prodrug B9207-015	
Protein binding	
Ciclesonide: RPR 257970 protein binding in plasma of various species and in isolated human plasma proteins	2003/0001
Serum protein binding of ciclesonide in different species, including humans	246/2001
Investigation of the enzymology of metabolism by human liver microsomes.	241E/98
Placental transfer	
Pharmacokinetics of metabolite B9207-021 in the female rabbit following a single subcutaneous and intravenous dose of ciclesonide	219/2000
Metabolism-in vitro	
Binding affinities of BYK199393 and BYK204147 (ciclesonide metabolites of the M4 family) in the glucocorticoid receptor binding assay	237/2001
In vitro metabolism of ciclesonide in the human lung and liver using precision-cut tissue slices	238/2001
In vitro metabolism of ciclesonide in the rat lung using precision-cut tissue slices	105/2001
Drug interactions	
Ciclesonide: In vitro CYP450 enzyme inhibition study of ciclesonide RM1 in human liver microsomes: determination of IC50 values and screening for metabolism-based inhibition	2002/064
Ciclesonide: Assessment of in vitro CYP450 enzyme induction potential of ciclesonide in primary cultures of human hepatocytes	2003/0078
Toxicokinetics	
Toxicity of ciclesonide R-epimer and <del> </del> in beagle dogs as dry powder aerosol inhalation for 3-months	131/2003
Pharmacokinetics of metabolite B9207-021 in the female rabbit following a single subcutaneous and intravenous dose of ciclesonide	219/2000
Reproductive toxicity:	
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	235/00
Other toxicity studies:	
28-Day endocrine toxicity study in rats treated with b9207-015 by inhalation	59/2001
Qualification for <del> </del> (impurity) in beagle dogs as dry powder aerosol inhalation for 3 months	131/2003*

b(4)

*impurity qualification study in dogs has been reviewed separately on 08/03/2004

Previous Reviewed Preclinical Studies in IND53391 and Submitted in this NDA:

Study	Location in Model 4	Date of Review
Primary Pharmacodynamics:		
Binding study of four compounds in estrogen, progesterone and testosterone receptor assays	45E/96	08/01/1997
Binding affinity of ciclesonide analogs to the glucocorticoid receptor of rat lung	123E/93	08/01/1997
Binding affinities of ciclesonide metabolites M2, M3a and M5 in the glucocorticoid receptor binding assay	266/99	12/07/2001
Inhibition of ConA-induced proliferation of human peripheral blood mononuclear cells by B9207-015, B9207-016, B9207-21, B9207-022, budesonide and dexamethasone	53/95	08/01/1997
Inhibition of CD3-mediated proliferation of human peripheral blood mononuclear cells by BYK20432, BYK20702, BYK54297, BYK55327 and BYK54609	7/99	12/07/2001
Inhibition of the IL-2 production of CD3-stimulated human peripheral blood mononuclear cells by B9207-015, B9207-016, B9207-21 and budesonide	90/94	08/01/1997
Inhibition of anti-CD3-induced cytokine synthesis in mouse Th2 lymphocytes by ciclesonide (B9207-015) and the ciclesonide metabolite B9207-021	45/94	08/01/1997
Attenuation of bradykinin-induced mucosal leakage in rat trachea by topical ciclesonide	67/95	08/01/1997
Effects of single intratracheal powder instillation of ciclesonide on cell accumulation in BAL of ovalbumin-sensitized Brown-Norway rats.	112/96	08/01/1997
Reduction of croton oil-induced mouse ear edema by R-epimer of ciclesonide and its metabolite B9207-021	80/94	08/01/1997
Secondary Pharmacodynamics:		
Comparison of the antiproliferative activity of ciclesonide and its epimers after local administration in the rat (cotton pellet granuloma test)	202/93K	08/01/1997
Effects on renal function and serum glucose after single intraperitoneal administration	37/96	03/20/1998
Safety Pharmacology:		
Influence of B9207-015 i.v. on behavior of female mice	96/94	08/01/1997
Influence of B9207-015 i.v. on behavior of female rats	95/94	08/01/1997
Hemodynamic and respiratory effects of B9207-015, administered as i.v. infusion to anesthetized cats	99/94	08/01/1997
Pharmacokinetics:		
Pharmacokinetics of [14C]-ciclesonide in the dog following a single intravenous and oral dose	93/96	08/01/1997
Tissue distribution of [14C]-ciclesonide in the rat following a single intravenous, oral and intratracheal dose	117/96	08/-1/1997

Whole-body autoradiographic study of [¹⁴ C]-ciclesonide in the rat following a single intravenous and oral dose	214/99	12/07/2001
Placental transfer and mammoglandular passage of [¹⁴ C]-ciclesonide in the rat	172/99	12/07/2001
Metabolism, in vitro		
In vitro metabolism of [¹⁴ C]-ciclesonide by animal and human liver microsomes	71/98	06/18/2001
Binding affinities of ciclesonide metabolites M2, M3a and M5 in the glucocorticoid receptor binding assay	266/99	12/07/2001
Investigation of the in vitro formation of the major ciclesonide metabolite 1.	10/96	08/01/1997
In vitro metabolism of ciclesonide in the dog using precision-cut slices and liver microsomes	280/99	12/07/2001
Toxicokinetics:		
Toxicokinetics of ciclesonide in a 4-week inhalation toxicity study in Sprague-Dawley rats (aerosol generated from powder)	197/97	03/20/1998
Toxicokinetics of ciclesonide in a 4-week inhalation toxicity study in Wistar rats (aerosol generated from MDI)	199/97	03/20/1998
Toxicokinetics of ciclesonide in a 6-month inhalation toxicity study in Sprague-Dawley rats (aerosol generated from powder)	198/97	03/20/1998
Toxicokinetics of ciclesonide in a 6-month oral toxicity study in Wistar rats	222/97	06/18/2001
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	06/18/2001
Toxicity of ciclesonide in beagle dogs following inhalation as powder aerosol as DI generated aerosol for 3 months	273/98	12/07/2001
Toxicokinetics of ciclesonide and metabolite B9207-021 in a 3-month inhalation toxicity study in beagle dogs (aerosol generated from MDI and powder)	19/99	12/07/2001
Toxicokinetics of ciclesonide and metabolite B9207-021 in a 1-year inhalation toxicity study in beagle dogs (aerosol generated from powder)	221/97	06/18/2001
Toxicokinetics of ciclesonide and metabolite B9207-021 in a 1-year oral toxicity study in beagle dogs	238/98	06/18/2001
Carcinogenic Toxicokinetics:		
Toxicokinetics of Ciclesonide in an oral carcinogenicity study in mice	282/2000	05/24/2004
Toxicokinetics of Ciclesonide in an inhalative carcinogenicity study in Wistar rats (aerosol generated from metered dose inhalers)	177/99	05/24/2004
Single-Dose Toxicity:		
Single dose toxicity after oral administration of B9207-015	94/94	08/01/1997
Single dose toxicity after intraperitoneal administration of B9207-015 to mice	164/94	08/01/1997
Single dose toxicity after oral administration of B9207-015 to	106/94	08/01/1997

rats		
Single dose toxicity after intraperitoneal administration of B9207-015 to rats	165/94	08/01/1997
Repeat-Dose Toxicity:		
28-Day inhalation study of B9207-015 in Sprague-Dawley rats	121E/94	08/01/1997
28-Day dose range finding inhalation study of B9207-015 in Sprague-Dawley rats	167E/96	08/01/1997
28-Day inhalation toxicity study of B9207-015 in metered dose inhaler (MDI) in Wistar (WU) rats	92E/97	11/05/1997
6-Month inhalation study of B9207-015 in Sprague-Dawley rats	138E/95	08/01/1997
The toxicity of B9207-015 after oral administration in the rat for 4 weeks	76/94	09/05/1997
The toxicity of B9207-015 after oral administration in the rat for 6 months	223/95	09/05/1997
Ciclesonide-subchronic toxicity in the rat after subcutaneous administration (28 days)	112E/94	09/05/1997
Ciclesonide-chronic toxicity in the rat after subcutaneous administration (6 months)	113E/94	09/05/1997
Toxicity of B9207-015 in beagle dogs following inhalation for 4 weeks	205/94	08/01/1997
Toxicity of B9207-015 in beagle dogs following inhalation from MDI (metered dose inhaler) for 4 weeks	103/97	11/5/1997
Toxicity of ciclesonide in beagle dogs following inhalation as powder aerosol/as MDI generated aerosol for 3 months	273/98	12/07/2001
Toxicity of B9207-015 in beagle dogs following inhalation for 12 months	116/96	08/01/1997
Ciclesonide-subchronic toxicity in the dog after inhalation (28 days)	114E/94	08/01/1997
Ciclesonide-chronic toxicity in the dog after inhalation (6 months)	115E/94	08/01/1997
Toxicity of B9207-015 in beagle dogs following oral administration for 4 weeks	75/94	09/05/1997
Toxicity of B9207-015 in beagle dogs following oral administration for 12 months	136/98	03/01/1999
The toxicity of B9207-015 in beagle dogs following intravenous administration for 2 weeks per infusion	154/94	09/05/1997
Genotoxicity:		
Reverse mutation test of ciclesonide in bacteria	44E/99	12/07/2001
Assessment of mutagenic potential in histidine autotrophs of salmonella typhimurium (Ames test)	107E/94	08/01/1997
Action of B9207-015 on mutations affecting the hypoxanthine-guanine phosphoribosyl transferase locus in V79 cells (HGPRT test)	209/95	08/01/1997
Chromosome aberration assay in human lymphocytes in vitro with B9207-015	111/94	08/01/1997
Testing of B9207-015 for mutagenic activity in the mouse by	100/95	08/01/1997

means of the micronucleus test		
Micronucleus test with v79 cells in vitro with B9207-015	80/97	08/01/1997
Testing of B9207-015 for mutagenic activity in the mouse by means of the micronucleus test (second study)	161/95	08/01/1997
Testing of B9207-015 for mutagenic activity in the mouse by means of the micronucleus test with oral administration (third study)	161/96	08/01/1997
Mouse micronucleus test: comparison between ciclesonide, budesonide, and dexamethasone with oral administration	75/96	08/01/1997
Carcinogenicity:		
The toxicity of B9207-015 after oral administration in the mouse for 3 months (dose range finding)	185/95	07/08/1998
The toxicity of B9207-015 after oral administration in the mouse for 3 months (dose range finding, second study)	20/97	07/08/1998
B9207-015 (ciclesonide)-Carcinogenicity study by oral administration to B6C3F1 mice for 104 weeks	281/2000	05/24/2004
Carcinogenicity inhalation study of B9207-015 in metered dose inhaler (MDI) in Wistar (WU) rats	176E/99	05/24/2004
Reproductive Toxicity:		
Influence on male and female fertility (rat). Effects on early embryo-fetal development. Toxicity of B9207-015 for reproduction after oral administration	153/97	06/18/2001
Toxicity of B9207-015 for reproduction after oral administration. Study for effects on embryo-fetal development in the rat.	109/95	08/01/1997
Toxicity of B9207-015 for reproduction. Study for effects on embryo-fetal development in the rabbit s.c.	106/95	08/01/1997
Other Toxicity Studies:		
Hemolytic potential of B9207-015 in beagle dogs following short-term intravenous administration	33/95	09/05/1997
Study on primary irritation of B9207-015 in the guinea pig	123/94	09/05/1997
Local toxicity of B9207-015 after a single intravenous, paravenous or intra-arterial injection in the rabbit.	72/95	09/05/1997
Influence of B9207-015 on erythrocyte stability in vitro	8/95	09/05/1997
Test for sensitizing properties of B9207-015 in the guinea pig	122/94	08/01/1997
Antigenicity study of ciclesonide in guinea pig (ASA, PCA reaction)	48E/99	12/07/2001
Antigenicity study of ciclesonide in mice-rats (PCA reaction)	49E/99	12/07/2001

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Deliberative Process (b5)

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Ciclesonide is a pro-drug as shown by 120-fold higher binding affinity of its de-esterified metabolite to glucocorticoid receptor. The drug was shown to have pharmacodynamic activity relevant to asthma in animals. In rat ex vivo model, ciclesonide inhibited bradykinin-induced mucosal leakage in trachea. Intratracheal administration of ciclesonide reduced cell accumulation and protein concentration in bronchoalveolar lavage (BAL) in ovalbumin sensitized rats, and inhibited sephadex-induced lung edema in rats. Additionally, inhalation of ciclesonide reduced airway hyper-responsiveness to allergen (measured by methacholine concentration to induce 200% lung resistance). In vitro, ciclesonide inhibited lymphocyte proliferation induced by Concanavalin (rat spleen cells and human peripheral mononuclear cells) and anti-CD3 (human PBMC); inhibited CD-3 mediated release of IL-4 and IL-5 by mouse Th2 cells and IL-2 release by CD3-Stimulated Human Peripheral Blood Mononuclear Cells (PBMCs).

b(4)

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

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

The mechanisms by which ciclesonide alleviate asthma are not completely understood. As a glucocorticoid, it was hypothesized via suppression of immune response and airway hypersensitivity. Several in vitro and in vivo studies demonstrated that ciclesonide inhibited lymphocyte proliferation, inhibited release of cytokine (IL-2, IL-4, IL-5, TNF α and IFN- γ), inhibited inflammatory cells (including eosinophils) and protein accumulation in lower airway, and reduced lung edema and mucosal leakage in trachea. Ciclesonide also inhibits the allergen-induced airway hyperresponsiveness.

Drug activity related to proposed indication:

1. In vitro studies

- Receptor binding studies

In the presence of esterase inhibitors, the affinity to the human glucocorticoid receptor was 120-fold higher for metabolite RM1 (product of ester bond cleavage) than for ciclesonide itself. The glucocorticoid receptor binding affinity of RM1 was similar to that of budesonide and fluticasone (see the table below for details)

Binding affinity for the human glucocorticoid receptor	
glucocorticoid	Ki (nmol/L)
Ciclesonide	37
RM1	0.310
Budesonide	0.438
Fluticasone	0.238

A study with rat glucocorticoid receptors confirmed the results in the human glucocorticoid receptors. In this study, S-epimer was also investigated and the S-epimer was observed with 6-fold lower binding affinity than R-epimer. The metabolite SM1 of S-epimer had higher binding affinity than the S-epimer. The data are summarized in the Table below.

Relative binding affinity (RBA) for the glucocorticoid receptor of rat lung cytosol	
Glucocorticoid	RBA
Dexamethasone	100
R/S-Budesonide	900
R-Ciclesonide	12
RM1	1200
S-Ciclesonide	2
SM1	230

Results represent means of duplicate determinations and are normalized relative to dexamethasone which was set as 100.

RM1 has the greatest affinity for the glucocorticoid receptor among the metabolites derived from ciclesonide. Further metabolism of RM1 resulted in much less active metabolites including M2, M3a, M5 and M4 family.

- Inhibition of cell lymphocyte and monocyte proliferation and inhibition of cytokine release by these cells
Several in vitro studies demonstrated that ciclesonide and RM1 inhibit lymphocyte proliferation and cytokine release. In most of these studies ciclesonide was 6-fold less potent than RM1 which had similar potency to budesonide but less potent than fluticasone. The table below presents these study results.

Test system		Cicles.	RM1	Budes.	Flutic.
Con-A induced rat spleen cell proliferation	IC ₅₀ nM	1.90*	1.44*	1.31*	-
Con-A induced human PBMC proliferation	IC ₅₀ nM	10.8*	1.3*5	1.65*	-
Anti-CD3 induced human PBMC proliferation	IC ₅₀ nM	-	2.39*	2.23*	0.27*
Anti-CD3 induced IL-2 release from human PBMC	IC ₅₀ nM	4.5*	0.7*	1.3*	-
Anti-CD3/CD28 induced human CD4+ responses:					
Proliferation	IC ₄₀ nM	1.37	0.23	1.31	0.09
IL-2 release	IC ₄₅ nM	0.71	0.17	0.23	0.05
IL-4 release	IC ₃₅ nM	0.81	0.78	0.26	0.09
IL-5 release	IC ₄₅ nM	0.53	0.19	0.20	0.04
Anti-CD3 induced IL-4 release in mouse Th2 cells	IC ₅₀ nM	0.42	0.19	0.32	-
Anti-CD3 induced IL-4 release in mouse Th2 cells	IC ₅₀ nM	0.27	0.12	0.22	-
LPS-induced TNF α release from human whole blood	IC ₃₅ nM	900	30	10	10
LPS-induced TNF α release from human monocytes	IC ₃₅ nM	>1000	53	13	-
LPS-induced TNF α release from human dendritic cells	IC ₄₅ nM	80	12	5	-

Cicles.=ciclesonide, Budes.=budesonide, flutic.=fluticasone, *average value from 2-4 experiments, - not investigated

2. In vivo studies

- Inhibition of bradykinin-induced mucosal leakage in situ: At doses of 1-100 μ M for R-ciclesonide and 3-300 μ M of Budesonide, there was 23-40% and 9-35% inhibition of leakage in trachea, respectively. The IC₂₅ values were 14.7 and 39.5 μ M, respectively, for R-ciclesonide and budesonide.
- Reduction of allergic lung inflammation: In ovalbumin sensitized rats, intratracheal administration of ciclesonide at doses of 1.0 and 10.0 mg/kg inhibited total cells (53-89%), neutrophils (43-86%), lymphocytes (52-64%) and eosinophils (66-96%) accumulation, as well as influx of protein (43-91%) in lower airway (BAL). The study was repeated with slight different dosing regimens and ED₅₀ values of ciclesonide, RM1, and budesonide from the two studies are as follows.

Effect of intratracheal administration of ciclesonide and RM1 to lungs in OVA sensitized rats

Dosing time ¹	Measuring time ²	parameter	ED50 (mg/kg, i.t.)			
			Ciclesonide	RM1	Budesonide	fluticasone
18 hrs	27 hrs	Neutrophils in BAL	1.46		0.97	-
		Eosinophils in BAL	0.26		<0.1	-
		Protein in BAL	0.95		0.14	-
24+1 hrs	48 hrs	Total cells in BAL	0.6	0.7	0.5	
		Neutrophils in BAL	0.3	0.8	0.9	
		Eosinophils in BAL	0.5	0.7	1.3	
		Protein in BAL	0.6	0.5	0.7	
24+1 hrs	24 hrs	Eosinophils in BAL	0.75	1.97		0.095
		Eosinophils in lung tissue	0.49	1.00		0.068

¹ time before antigen challenge, ² time after antigen challenge

- Sephadex intratracheal administration to rats induces lung edema. Administration of the ciclesonide (or RM1 or fluticasone) 24 hours before and together with sephadex significantly reduced lung edema. ED₅₀ values for edema reduction by ciclesonide, RM1 and fluticasone were 0.72, 1.08 and 0.08 mg/kg, respectively.
- Inhibition of airway hyper-responsiveness: In ovalbumin sensitized rats, inhalation of ciclesonide at 1-6.19 µg/kg (pulmonary deposited doses) for consecutive 3 days before allergen challenge resulted in 66-86% reduction of immediate (7 minutes) and 39-93% reduction of late (3-6 hours) airway response. In these rats, lung inflammatory cell influxes induced by allergen were also reduced by ciclesonide treatment (↓50-89% in total leukocytes, ↓56-93% in eosinophils, ↓41-75% in neutrophils and ↓100% mononuclear cells). With the same animal model, reduced PC₂₀₀ (methacholine concentration to induce 200% lung resistance) was partially recovered by ciclesonide treatment (PC₂₀₀ was 522 µg/ml in non-sensitized control animals, 84 mg/ml in sensitized animals and 354 µg/ml in sensitized animals receiving ciclesonide at 6 µg/kg pulmonary dose).

2.6.2.3 Secondary pharmacodynamics

1. Anti-inflammatory activities:

- Croton oil induced mouse ear edema: In this model, ear edema was reduced by topical administration of ciclesonide (18-68% by 1-100 µg/ear) and RM1 (14-59% by 1-100 µg/ear). Budesonide was more potent as seen that the doses of 1-100 µg/ear inhibited 60-72% of edema.
- Subcutaneous cotton implantation provoked local granuloma formation (proliferation activity) and increase in pellet weight: Glucocorticoid contained in cotton pellet significantly reduced the inflammatory response. The ED₅₀ values for local granuloma inhibition for ciclesonide, RM1, and budesonide were 2 µg/pellet, 40.8 µg/pellet, and 33.48µg/pellet, respectively.

2.6.2.4 Safety pharmacology

There were no toxicity findings in safety pharmacology studies in CNS, cardiovascular and respiratory system, and renal function (See Attachment 1, page 10, Attachment 4, page 4 and Attachment 7, page 3).

Neurological effects:

Ciclesonide had no effects on the behavior (Irwin test) of either female mice or female rats after an intravenous dose of 20 mg/kg.

Cardiovascular effects:

In conscious male dogs and anesthetized male cats, 15 min i.v. infusion at dose of 0.1, 0.3 and 1.0 mg/kg did not induce noticeable cardiovascular effects (blood pressure, heart rate, and ECG parameters)

Pulmonary effects:

The effects of ciclesonide on the respiratory system were studied in anesthetized male cats. Ciclesonide at IV doses of 0.1 to 1.0 mg/kg did not induce respiratory effects (respiratory rate, tidal volume or respiratory minute volume).

Other effects:

- The affinity to other steroid receptors was investigated for this drug in two independent series of experiments in the presence of esterase inhibitor. These two sets of experiments showed the similar results with regard to binding affinities for the receptors of estrogen, progesterone, and testosterone. Ciclesonide and RM1 had no detectable binding for human estrogen receptor and very low affinity to progesterone receptor and testosterone receptor (ciclesonide with 58-fold lower and RM1 with 577-fold lower affinity for progesterone than for glucocorticoid receptor, RM1 with 477-fold lower affinity for testosterone than for glucocorticoid receptor). S-ciclesonide and SM1, tested in one of the two sets of experiments, were observed with binding properties for these receptors similar to Ciclesonide and RM1. The following table presents the study results from one set of experiment.

Binding characteristics of ciclesonide, RM1, budesonide and fluticasone for various steroid hormone receptors

	Ki (nM)			
	Glucocorticoid receptor	Progesterone receptor	Testosterone receptor*	Estrogen receptor
Ciclesonide	37	2160	>10000	>10000
RM1	0.310	179	148	>10000
Budesonide	0.438	72	503	>10000
Fluticasone	0.238	296	>10000	>10000
R5020	-	4.0	-	-
Mibolerone	-	-	1.5	-
17- β -estradiol	-	-	-	0.16

All receptors were from human except the testosterone receptors which were from rats

Interestingly, a strong progesterone agonistic effect of ciclesonide was observed in a preliminary vitro study (single experiment). In this experiment, human mammary T47D cells transfected with a mouse mammary tumor virus (MMTV)-CAT construct were incubated with RM1 and budesonide and both steroids stimulated expression of CAT with an ED₅₀ of approximately 50 pM. That is, at concentrations much lower than the K_i values seen in the progesterone receptor binding assay, ciclesonide and budesonide showed progesterone-like agonist property. However, the sponsor reported that clinical trials have shown no effect on menstruation and this result was considered overestimated the progesterone-like agonist properties of ciclesonide.

- Inhibition of body weight gain, thymus involution, adrenal gland involution were common findings with administration of ciclesonide and other glucocorticoids. Additionally, intratracheal administration of ciclesonide to rats for 7 days resulted in reduction of femoral growth plate width (resorption within metaphyses due to osteoclast action bordering the hypertrophic zone) reduction of osteocalcin levels. For most of these systemic effects, ciclesonide was less potent than RM1 and fluticasone. The following table presents the systemic effects of glucocorticoids including ciclesonide in naïve rats.

Systemic effects in naïve rats following intratracheal administration of glucocorticoids for 7 days

	Effective dose (mg/kg/day)			Potency relative to ciclesonide	
	Ciclesonide	RM1	Fluticasone	RM1	Fluticasone
Inhibition of body weight gain (ED ₅₀)	0.2	0.09	0.02	2	10
Thymus involution (ED ₅₀)	0.32	0.16	0.05	2	6
Adrenal involution (ED ₂₅)					
Femoral growth plate (ED ₂₀)	3.11	0.99	0.07	3	44
Serum osteocalcin (ED ₂₀)	0.87	0.09	0.04	10	22
	2.98	5.89	0.36	0.5	8

- Mineralocorticoid activities: In rats, single intraperitoneal administration of 0.1-10 mg/kg ciclesonide had no effects on urine volume, pH, osmolarity and electrolytes (sodium, potassium, calcium, chloride), as well as on serum glucose. Oral administration of ciclesonide for 28 days in rats had no effects on sodium, potassium or chloride concentrations. In disagreement with the Sponsor, however, these data are of limited value because these results may reflect the low bioavailability of the oral and intraperitoneal administration rather than the effects on mineralocorticoid activities.

2.6.2.5 Pharmacodynamic drug interactions

Not performed.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

The following tables are scanned photos from the submission.

Primary pharmacodynamics		Test Article: Ciclesonide						
Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Glucocorticoid receptor binding affinity	Rat lung glucocorticoid receptors	Displacement of radio-labeled triamcinolone acetonide in the presence of disopropylfluoro phosphate (esterase inhibitor), relative binding affinity (RBA) versus dexamethasone.	Not given	--	Ciclesonide: RBA=12 RM1: RBA=1200 Dexamethasone: RBA=100	no	123E/93	Study 123E/93
Glucocorticoid receptor binding affinity of metabolites: B-ring-hydroxylated RM1, cyclohexane-hydroxylated RM1 and 4,5-dihydro RM1,	Rat glucocorticoid receptor	Displacement of radio-labeled triamcinolone acetonide from human glucocorticoid receptor, preparation of metabolites using rat and guinea pig liver cell fractions and HPLC purification.	0.3 nmol/L to 10 µmol/L	--	The receptor binding affinity of the metabolites, B-ring-hydroxylated RM1, cyclohexane-hydroxylated RM1 and 4,5-dihydro RM1, were considerably lower than for dexamethasone and RM1	no	266/99	Study 266/99
Glucocorticoid receptor binding affinity of fatty acid conjugates	Rat glucocorticoid receptor	Displacement of radio-labeled triamcinolone acetonide from human glucocorticoid receptor	1 nmol/L to 10 µmol/L	--	The receptor binding affinity of fatty acid conjugates was much lower than for dexamethasone	no	237/2001	Study 237/2001

Primary pharmacodynamics

Test Article: Ciclesonide

Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Glucocorticoid receptor transactivation/transrepression and progesterone receptor activity of RM1	HeLa cells	Transactivation was determined using HeLa cells transfected with MMTV-luciferase linked to glucocorticoid receptor. Transrepression was assessed in HeLa cells by collagenase I-mRNA detection following phorbol ester stimulation. Effect on progesterone receptor activation was investigated using T47D cells, stably transfected with MMTV-CAT.	0.0001 to 100 nmo/L	-	RM1: No differences in transactivation or transrepression pattern compared to budesonide or fluticasone. Ciclesonide and budesonide seem to be progesterone receptor agonists.	no	204/2001	Study 204/2001
Inhibition of Concanavalin A-stimulated spleen cell proliferation	Rat spleen cells	Proliferation of purified spleen cells was assessed 72 h following stimulation using an MTT assay	0.01 to 1000 nmo/L	-	Ciclesonide: The Con A-stimulated spleen cell proliferation was inhibited in a concentration dependent manner. In three independent experiments the IC50 values were 1.399, 1.591 and 2.700 nmo/L. RM1 had a similar potency in this assay. In three independent experiments the IC50 values were 1.265, 1.373 and 1.686 nmo/L.	no	89/94	Study 89/94

Primary pharmacodynamics

Test Article: Ciclesonide

Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Inhibition of Concanavalin A-stimulated proliferation of human peripheral blood mononuclear cells	Human PBMC	Proliferation of purified PBMC was assessed 72 h following stimulation by 3H-thymidine or bromodesoxyuridine incorporation	0.01 to 1000 nmo/L	-	Ciclesonide: The Con A-stimulated PBMC proliferation was inhibited in a concentration dependent manner. In four independent experiments the IC50 values were 14.61, 5.421, 6.162 and 17.08 nmo/L. RM1 had a higher potency in this assay. In four independent experiments the IC50 values were 1.367, 0.9822, 1.12 and 1.903 nmo/L.	no	53/95	Study 53/95
Inhibition of CD3-mediated proliferation of human peripheral blood mononuclear cells	Human PBMC	Proliferation of purified PBMC was assessed 72 h following stimulation by 3H-thymidine incorporation	0.01 to 1000 nmo/L	-	RM1: The CD3-mediated PBMC proliferation was inhibited in a concentration dependent manner. In four independent experiments the IC50 values were 2.37, 0.85, 3.33 and 3.01 nmo/L.	no	7/99	Study 7/99

Test Article: Ciclesonide

Primary pharmacodynamics								
Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Inhibition of CD3-stimulated IL-2 release from human peripheral blood mononuclear cells	Human PBMC	IL-2 release from purified PBMC was assessed 24 h following stimulation using the ELISA technique	0.01 to 1000 nmol/L	--	Ciclesonide: The CD3-mediated IL-2 release was inhibited in a concentration dependent manner. In two independent experiments the IC50 values were 2.599 and 6.370 nmol/L. RM1: The CD3-mediated IL-2 release was inhibited in a concentration dependent manner. In two independent experiments the IC50 values were 0.013 and 1.345 nmol/L.	no	90/94	Study 90/94
Inhibition of CD3-stimulated IL-4 and IL-5 release from murine Th2-type lymphocytes	Murine Th2-type lymphocytes (D10.G4.1 cell line)	IL-4 and IL-5 release from murine Th2-type cells in co-culture with murine splenocytes was assessed 16 h following stimulation using the ELISA technique	0.03 to 3 nmol/L	--	Ciclesonide: The CD3-mediated IL-4 as well as IL-5 release was inhibited in a concentration dependent manner. The IC50 values for IL-4 and IL-5 were 0.42 and 0.27 nmol/L, respectively. RM1: The CD3-mediated IL-4 as well as IL-5 release was inhibited in a concentration dependent manner. The IC50 values for IL-4 and IL-5 were 0.019 and 0.12 nmol/L, respectively.	no	45/94	Study 45/94

Test Article: Ciclesonide

Primary pharmacodynamics								
Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Inhibition of anti-CD3/CD28-stimulated lymphocyte function	Human CD4+ lymphocytes from whole blood	Proliferation, IL-2, IL-4, IL-5 and INF γ release from purified blood CD4+ lymphocytes was assessed 72 h following stimulation using 3H-thymidine incorporation and ELISA technique, respectively	0.001 to 1000 nmol/L	--	Ciclesonide: All parameters were inhibited in a concentration dependent manner. The half maximum inhibition ranged from 35 to 45 %; the values for proliferation, IL-2, IL-4, IL-5 and INF γ release were 1.37, 0.71, 0.81, 0.53 and 1.51 nmol/L, respectively. RM1: All parameters were inhibited in a concentration dependent manner. The half maximum inhibition ranged from 35 to 45 %; the values for proliferation, IL-2, IL-4, IL-5 and INF γ release were 0.23, 0.17, 0.78, 0.19 and 0.38 nmol/L, respectively.	no	61/2001	Study 61/2001

Primary pharmacodynamics **Test Article: Ciclesonide**

Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Inhibition of LPS-induced TNF α release from human whole blood	Human whole blood	Stimulation with LPS, after 4 h measurement of TNF α using the ELISA technique	0.001 to 1000 nmol/L	–	Ciclesonide inhibited the LPS-induced TNF α release in a concentration dependent manner, the IC35 was 900 nmol/L. RM1 inhibited the LPS-induced TNF α release in a concentration dependent manner, the IC35 was 30 nmol/L	no	271/2000	Study 271/2000
Inhibition of LPS-induced TNF α release from human monocytes and dendritic cells	Monocytes from human whole blood and monocytes derived dendritic cells	Stimulation with LPS, after 13 h (monocytes) or 24 h (dendritic cells) measurement of TNF α using the ELISA technique	0.1 to 1000 nmol/L	–	Ciclesonide had no effect on LPS-induced TNF α release from monocytes but inhibited TNF α release from dendritic cells in a concentration dependent manner, the IC45 was 80 nmol/L. RM1 inhibited the LPS-induced TNF α release from monocytes and dendritic cells in a concentration dependent manner. The IC30 was 53 nmol/L and the IC45 was 12 nmol/L, respectively.	no	274/2000	Study 274/2000

Primary pharmacodynamics **Test Article: Ciclesonide**

Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Inhibition of bradykinin-induced mucosal leakage	Rat Sprague Dawley	Bradykinin superfusion-induced bronchial mucosal leakage was assessed due to Evans blue extravasation	1, 10, 30 and 100 μ mol/L in superfusion fluid	7-8	Ciclesonide inhibited dose-dependently the bradykinin-induced mucosal leakage after topical administration, the IC25 was 14.7 μ mol/L	no	67/95	Study 67/95
Inhibition of bradykinin-induced mucosal leakage, budesonide	Rat Sprague Dawley	Bradykinin superfusion-induced bronchial mucosal leakage was assessed due to Evans blue extravasation	3, 30 and 300 μ mol/L in superfusion fluid	8	Budesonide inhibited dose-dependently the bradykinin-induced mucosal leakage after topical administration, the IC25 was 39.5 μ mol/L	no	193/94	Study 193/94
Effect on cell accumulation and protein concentration in 48 h BAL	Rat Brown-Norway	Bronchoalveolar lavage 48 h after ovalbumin challenge; determination of total cell number, eosinophils, neutrophils and lymphocytes, TNF α and protein concentration	0.1, 0.3, 1, 3 and 10 mg/kg intratracheal, 24 h and 1 h before challenge	8; 16	Ciclesonide: ID50 (mg/kg): total cells 0.6, lymphocytes 0.9, neutrophils 0.3, eosinophils 0.5, protein 0.8 and TNF α 0.4. RM1: ID50 (mg/kg): total cells 0.7, lymphocytes 0.7, neutrophils 0.8, eosinophils 0.7, protein 0.5 and TNF α 0.4	no	49/2001	Study 49/2001
Effect on cell accumulation and protein concentration in 27 h BAL	Rat Brown-Norway	Bronchoalveolar lavage 27 h after ovalbumin challenge; determination of total cell number, eosinophils, neutrophils and lymphocytes and protein concentration	0.1, 1 and 10 mg/kg intratracheal, single dose 1 h before challenge	10	Ciclesonide: ID50 (μ mol/kg): total cells 1.43, neutrophils 2.71, eosinophils 0.49 and protein 1.75	no	112/96	Study 112/96

Primary pharmacodynamics **Test Article: Ciclesonide**

Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Effect on cell accumulation and protein concentration in 27 h BAL, budesonide	Rat, Brown-Norway	Bronchoalveolar lavage 27 h after ovalbumin challenge; determination of total cell number, eosinophils, neutrophils and lymphocytes and protein concentration	0.1, 1 and 10 mg/kg intratracheal, single dose 1 h before challenge	10	Budesonide: ID50 (µmol/kg): neutrophils 2.26, eosinophils <0.23 and protein 0.32	no	72/98	Study 72/96
Inhibition of airway hyperresponsiveness to methacholine	Rat, Brown-Norway	Determination of airway hyperresponsiveness from changes of airway resistance to increasing concentrations of methacholine (15.625-1000 µg/ml) in actively sensitized and challenged rats	6.0 µg/kg once daily by inhalation for 3 days	12	Ciclesonide inhibited the allergen-induced airway hyperresponsiveness following the repeated inhalation administration of 6.0 µg/kg once daily for 3 days. The PC200 values for the ciclesonide treatment group, positive and negative controls were 354.3, 521.6 and 84.1 µg/ml methacholine, respectively.	no	128/2001	Study 128/2001
Inhibition of allergic early and late phase bronchoconstriction and cell accumulation in BAL	Rat, Brown-Norway	Lung function measurement within 7 min after allergen challenge (early phase) and up to 6 h (late phase), determination of total cell number, eosinophils, neutrophils and mononuclear cells	1.00, 3.29 and 6.19 µg/kg once daily by inhalation for 3 days	12	Ciclesonide inhibited the early and late phase bronchoconstriction and cell influx into the airway lumen in a dose-dependent manner (statistically significant).	no	129/2001	Study 129/2001

Primary pharmacodynamics **Test Article: Ciclesonide**

Principle of Test	Biolog. Material/Species	Notes to the Method	Concentration / Dose	No. per Group	Noteworthy Findings	GLP	Study Report	Location in Module 4
Effect on lung eosinophil accumulation 24 h after challenge	Rat, Brown-Norway	Bronchoalveolar lavage and preparation of lung tissue 24 h after ovalbumin challenge; determination of total cell number, eosinophils, neutrophils, lymphocytes and mononuclear cells	Ciclesonide 0.1, 0.3, 1, 3, 10 mg/kg, RM1 0.3, 1, 3 and 10 mg/kg intratracheal, 24 h and 1 h before challenge	12	Ciclesonide inhibited the allergen-induced lung eosinophilia in a dose dependent manner. The ED50 values for lung tissue and BAL fluid were 0.49 and 0.75 mg/kg, respectively. RM1 was less potent in this model. The ED50 values for lung tissue and BAL fluid were 1.00 and 1.97 mg/kg, respectively.	no	2001-1531	Study 2001/1531
Effect on sephadax induced lung edema	Rat, Sprague-Dawley	Measurement of wet lung weight 24 h after intrapulmonary sephadax instillation, determination of thymus weight and body weight loss	0.03, 0.1, 0.3, 1, 3 and 10 mg/kg intratracheal, 24 h and 0 h before challenge	8	Ciclesonide inhibited the sephadax induced lung edema in a dose dependent manner, the ID50 value was 0.72 mg/kg. RM1 had a similar potency in this model, the ID50 value was 1.08 mg/kg. Ciclesonide and RM1 had a dose dependent effect on thymus involution and body weight reduction.	no	2001-1531	Study 2001/1531

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Oral administration of ciclesonide resulted in large absorption (28% in rats, 66% in dogs) but very low bioavailability due to an extensive first pass effect. The combined exposure to ciclesonide and RM1 was less than 6% of that given by intravenous route in most animals.

Both ciclesonide and RM1 have a large volume of distribution (4-6L/kg in rats, mice and dogs). T_{1/2} of ciclesonide was short (1 hour in rats and mice) which is probably due to conversion of ciclesonide to RM1. T_{1/2} of RM1 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 RM1 were lung, heart, thyroid, adrenals, liver, and kidneys.

Ciclesonide is rapidly hydrolyzed (de-esterification) to active RM1 metabolite in the lung and in the circulation. RM1 was further metabolized into several products primarily by Cyp3A4. These metabolites are primarily hippuric acid, 4, 5-dihydro RM1, B-ring-hydroxylated RM1, isomer of dihydroxy RM1 and isomers cyclohexane-hydroxylated RM1. In lung, fatty acid conjugates of RM1 were also observed and were considered as an active drug reservoir based on the reversible nature of the conjugations. All of the metabolites of RM1 including fatty acid conjugates of RM1 had much less pharmacological activity than RM1 and were considered inactive.

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 RM1 does not induce or inhibit liver enzymes.

Both Ciclesonide and RM1 had about 99% of plasma binding in all species studied.

Toxicokinetics studies showed that, when given by inhalation, systemic exposures to ciclesonide and/or RM1 (AUC) was proportional to the doses and there were no drug accumulations over time by daily dosing.

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.

2.6.4.3 Absorption

¹⁴C-ciclesonide was rapidly absorbed after oral dosing and the absorption levels were 66% in dogs and 28% in rats (based on comparison on the plasma AUC of radioactivity in animals receiving the drug by oral and i.v). After both intravenous and oral dosing, ciclesonide was rapidly converted to the RM1 metabolite. However, in most animals, the oral exposures of ciclesonide and RM1, combined, was 6% or less relative to the exposure after intravenous administration due to extensive first-pass metabolism for both

compounds. The following table presents plasma PK data from single doses with i.v. and oral administrations in mice, rats, rabbits and dogs.

		Ciclesonide		RM1	
		i.v.	p.o.	i.v.	p.o.
Mouse	Dose (mg/kg)	0.75	0.75	0.75	0.75
	Tmax (hr)	0.083	ND	0.083	0.5
	Cmax (µg/l)	198	ND	109	0.3
	AUC (ng.h/ml)	82	ND	100	1.4
	T _{1/2} (hr)	1	ND	7	2.5
	Vss (L/kg)	5.1	-	-	-
	Abs. Bioavailability	-	-	-	1.4%
Rat	Dose (mg/kg)	0.5	0.5	0.5	0.5
	Tmax (hr)	0.083	ND	0.083	0.083
	Cmax (µg/l)	158	ND	73	0.29
	AUC (ng.h/ml)	64	ND	84	0.8
	T _{1/2} (hr)	1	ND	5	3.4
	Vss (L/kg)	4.2	-	-	-
	Abs. Bioavailability	-	-	-	0.95%
Rabbit	Dose (mg/kg)	0.02	0.1	0.02	0.1
	Tmax (hr)	0.083	ND	0.083	ND
	Cmax (µg/l)	0.64	ND	8.3	ND
	AUC (ng.h/ml)	ND	ND	13.5	ND
	T _{1/2} (hr)	ND	ND	2.4	ND
	Vss (L/kg)	ND	-	-	-
	Abs. Bioavailability	-	-	-	-
Dog	Dose (mg/kg)	0.1	0.5	0.1	0.5
	Tmax (hr)	0.25	0.42	0.38	0.79
	Cmax (ng/l)	121	4	18	3.8
	AUC (ng.h/ml)	36*	81*	29	8.4
	T _{1/2} (hr)	ND	ND	3.3	3.3
	Vss (L/kg)	-	-	-	-
	Abs. Bioavailability	-	-	-	-

*unreliable data as the ciclesonide was also detected in all pre-dose samples at an average concentration of 1.243 ng/ml. The source of contamination could not be identified and the levels of ciclesonide were considered undeterminable. The relative ratio of oral versus IV AUC_{0-∞} values of RM1 after oral IV and oral dosing of ciclesonide was 5.8% and this number (rather than combined ciclesonide and RM1) was considered as oral bioavailability in dogs.

It should be noted that in a previous review (Review 1, see Attachment 1), oral bioavailabilities of ciclesonide were inadvertently considered 66% in dogs and 28% in rats and they should be referred to absorption.

2.6.4.4 Distribution

The volume of distribution was obtained from single i.v. dose studies and the values of 5.1 L/kg in mice and 4.2 L/kg in rats for ciclesonide and 6L/kg in dogs for RM1 were reported.

After absorption, ciclesonide and/or RM1 were widely distributed in the body. Rats received a ¹⁴C-Ciclesonide intravenous dose showed that most drug-related radioactivity was associated with lungs, heart and thyroid. High concentrations of radioactivity were also observed in adrenals and the excretory organs, i.e., liver and kidneys. The brain and eyes contained very low levels of radioactivity. Fat and intestine started off with low concentrations of radioactivity, which increased until 4 hours but decreased to negligible levels by 24 hours. The concentrations of radioactivity were negligible after 24 hours in most tissues.

A study in pregnant rats receiving ¹⁴C-ciclesonide demonstrated that very small amount of drug passed placenta as evidenced by low radioactivities in fetus and amniotic fluid (tissue to plasma ratio of AUC were 0.4 and 0.2 for fetus and amniotic fluid, respectively. Whereas the ratio was 18.9 for both liver and lung). Pregnant rabbits given ciclesonide subcutaneously on day 29 post coitum were observed with 6-fold lower serum concentrations in the fetuses than the maternity on 3 hour post-dose.

Lactating rats given 0.16 mg/kg of ¹⁴C-ciclesonide by i.v. were observed with a appreciable amount of ¹⁴C-ciclesonide and/or its metabolites in milk and by 24 hours it was still higher that of most maternal tissues and was 25-fold of the plasma level. A similar profile of milk secretion was observed after an oral dose of 0.9 mg/kg in rats. However, it was reported that the cumulative amounts of radioactivities in milk over 24 hours following i.v. and oral dosing were 0.054% and 0.012 % of the dose (stated in the summary for PK section in the NDA submission but no such information was provided in the study report) (see Attachment 7).

Plasma protein bindings were studied for both RM1 and ciclesonide. RM1 at concentrations of 5-500 ng/ml had 99% protein binding in rat, dog, mouse, rabbit, and human plasma. Ciclesonide at 10-100 ng/ml had 99% protein binding with rat, dog, and human sera.

Drug distribution to red blood cells was studied in the mouse, rat, rabbit and dog. Red blood cell:serum ratios of radioactivity were mostly 0.5 or less at early time points, suggesting limited distribution to red blood cells after i.v. or oral administration.

2.6.4.5 Metabolism

Many in vitro, ex vivo and in vivo studies were conducted to investigate the metabolism of ciclesonide. These studies showed that ciclesonide was rapidly de-esterified into RM1. RM1 was further metabolized to hippuric acid, 4, 5-dihydro RM1, B-ring-hydroxylated RM1, isomer of dihydroxy RM1 and isomers cyclohexane-hydroxylated RM1. Minor amount of secondary glucuronic conjugates were also detected, as well as keto derivative of RM1 and double bond saturation derivative of cyclo-hydroxylated RM1. In human

studies, RM1 was the major circulating metabolite. The glucocorticoid receptor binding affinities of all metabolites from RM1 were much reduced compared to that of RM1. Among the metabolites of RM1, cyclohexane-hydroxylated RM1 was the most potent one which had about 25% binding affinity of that of RM1. However, in human in vivo studies, no cyclohexane-hydroxylated RM1 was detected in plasma. The binding affinities of ciclesonide metabolites to the glucocorticoid receptor are compared as the follows (the table is a scanned photo from the submission).

Metabolite	Relative IC ₅₀ (Dexamethasone = 1)
RM1	0.5
B-ring- hydroxylated RM1	7.6
Cyclohexane- hydroxylated (C-24) RM1	1.9
4, 5-Dihydro RM1	9.0

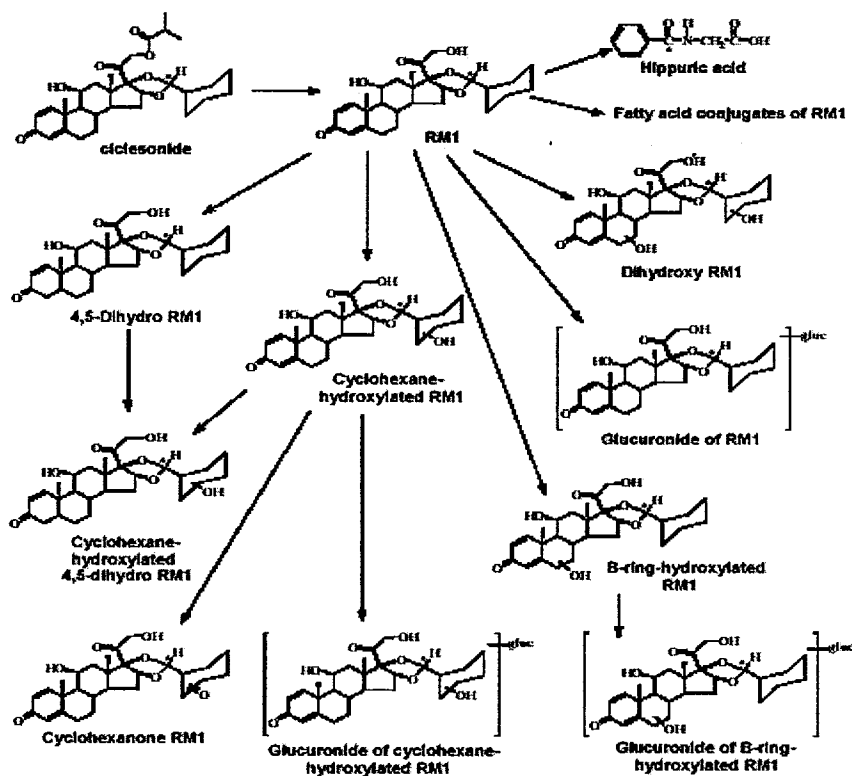
There were no qualitative differences observed in the metabolism of ¹⁴C-ciclesonide in the non-human species tests. All metabolites observed in human hepatocytes were also produced in hepatocytes from the species used in toxicology studies, indicating that the same metabolic pathways for ciclesonide were active in these species as are active in humans. The table below provides cross-species comparison of partial metabolites profiles (the table is a scanned photo from the submission).

Species	Matrix	RM1	Hippuric acid	Dihydroxy RM1	Cyclohexane-hydroxy RM1	B-ring-hydroxy RM1
Mouse	Serum	+	+	ND	ND	ND
	Urine	ND ¹	+	ND	ND	ND
	Feces	+	ND	ND	ND	ND
	Hepatocytes	+	ND	+	+	+
Rat	Serum	+	+	ND	-	ND
	Urine	ND	+	ND	-	ND
	Feces	+	ND	ND	ND	ND
	Hepatocytes	+	+	+	+	+
Rabbit	Plasma	+	-	ND	-	ND
	Urine	ND	+	ND	ND	ND
	Feces	+	ND	ND	+	ND
	Hepatocytes	+	+	+	+	+
Dog	Serum	+	+	ND	-	+
	Urine	ND	+	ND	ND	ND
	Feces	+	ND	ND	+	+
	Hepatocytes	+	ND	+	+	+
Human	Plasma	+	ND	ND	ND	ND
	Urine	ND	+	ND	ND	ND
	Feces	NA ²	NA	NA	NA	NA
	Hepatocytes	+	+	+	+	+

¹ND, not detected; ²NA, not analyzed; +, detected

Note: numerous additional minor metabolite peaks were observed; most of these remain unidentified. In *in vitro* animal hepatocyte studies glucuronide conjugates of RM1, cyclohexane-hydroxylated RM1 and B-ring-hydroxylated RM1, as well as a keto derivative of RM1 (which was also observed in rat serum), were identified.

The proposed metabolic pathway of ciclesonide is follows.



Incubation of ^{14}C -ciclesonide and ^{14}C -RM1 with human liver microsome confirmed that M1 is the first step product and this step was blocked by a carboxylesterase inhibitor. RM1 was the precursor for metabolites M2 (6-hydroxy derivative of M1) and M3 (hydroxyl derivative of M1 with $-\text{OH}$ group localized in the cyclohexyl moiety). The most extensive metabolism for RM1 was noted with CYP3A4. CYP 2D6m, 2CB and 4A11 played relatively minor or no role in the formation of M2 and M3.

Additionally, RM1 formed in lung partially forms fatty acid ester of RM1. In cultures with ciclesonide, RM1 oleate was observed in human lung slices, RM1 conjugates with oleate, palmitate, and linoleic acid were observed in rat lung slices. In culture with human liver slices, there were no fatty acid conjugate observed. The lipid conjugate of RM1 (oleate and palmitate) had less than 1% binding affinity to the glucocorticoid receptors, relative to dexamethasone and were considered to be inactive. The lipid conjugate is reversible as demonstrated by the conversion of 24% of total radioactivity to RM1 after an 18 h incubation of 25 μM synthetic C21-palmitate ester of RM1 in precision-cut rat lung slices. Therefore, the fatty acid conjugate formed in lung was considered as a reservoir for active drug.

2.6.4.6 Excretion

In rats, by oral or intravenous administration, most radio-labeled drug was excreted via feces (81-82% of dose) and small amount was via urine (8-9% of dose). Total recovered drug was 89-91% of dose. In dogs, similar excretion profile as to the rat was observed. The plasma clearance of ciclesonide or its metabolites in all species exceeded, or was similar to, the hepatic blood flow rate (ciclesonide: mice, 8.6 L.h/kg; rats, 7.4 L.h/kg. RM1: mice, 7.3 L.h/kg; rats, 5.9 L.h/kg; rabbits, 1.6 L.h/kg; dogs, 3.5 L.h/kg).

2.6.4.7 Pharmacokinetic drug interactions

Induction and inhibition of liver enzyme activity by Ciclesonide were studied.

In vitro incubation with human liver microsomes, RM1 at concentrations up to 3 μ M (about 400-fold higher than a C_{max} of 7.4 nM in human inhaled with 3.6mg/kg of ciclesonide) did not result in inhibition of more than 25% enzyme activity for any isoforms tested (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4).

Primary cultures of human hepatocytes in the presence of 0.01 μ M to 1 μ M of ciclesonide for three days showed that ciclesonide had no enzyme induction activities on Cyp 1A2, 2C9, 2C19 and 3A4.

Therefore, ciclesonide is unlikely to interact with other drugs through enzyme induction or inhibition.

2.6.4.8 Other Pharmacokinetic Studies

As both dry powder inhalation formulation (DPI) and metered dose formulation (MDI) were used in toxicology studies, TK profiles of DPI and MDI were compared in a 3-month study in dogs. In this study, similar plasma AUC (ciclesonide+RM1) and toxicities at the same doses were observed with these two different formulations. Details are in Attachment 7.

Toxicokinetics studies are included in each of the toxicology studies. Most of the studies were conducted by inhalation (MDI or DPI). Oral and subcutaneous routes were used for carcinogenesis and reproductive studies. In all of these studies, drug exposures (AUC of ciclesonide and RM1) were in a dose-proportional manner. There were no dose accumulations observed. No gender-specific findings were observed.

One TK study was provided in the current submission and reviewed as follows.

Pharmacokinetics in the female rabbit following a single subcutaneous and intravenous dose of ciclesonide

Key study findings: Bioavailability of ciclesonide given subcutaneously was about 80% in both nonpregnant and pregnant rabbits. Fetal drug concentrations were lower than maternal by a factor of about 6.

Research report #: 219/2000

Study/protocol: L15/FKM/103; LK0689

Volume #: eNDA 2.6.7.13.

Conducting Lab. and location: Animal experiments by Byk Gulden, Germany.

Analytics by ' _____'

Pharmacokinetics by Byk Gulden, Germany.

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Study period: 02/28/2000 -06/11/2000.

GLP compliance: Yes.

Quality assurance: Yes.

Drug, lot # and purity: Ciclesonide, Batch No. MG225/C, 98.1% purity.

Methods

"Little Russians" Rabbits were used in this study and the study design was as follows:

Non-pregnant animals:

Animal No.	Session I	Session II	Session III
1	i.v. 50µg/kg	s.c.25 µg/kg	s.c.100 µg/kg
2	i.v. 50µg/kg	s.c. 25 µg/kg	s.c. 100 µg/kg
3	i.v. 50µg/kg	s.c. 25 µg/kg	s.c. 100 µg/kg
4	s.c.25 µg/kg	i.v. 50µg/kg	s.c.100 µg/kg
5	s.c. 25 µg/kg	i.v. 50µg/kg	s.c. 100 µg/kg
6	s.c. 25 µg/kg	i.v. 50µg/kg	s.c. 100 µg/kg

There was a wash-out period of 2 weeks between sessions I and II. Session III was carried out about 6 weeks later.

Pregnant animals:

These animals (animal No's 7-10) received a single s.c. dose of 100 µg/kg ciclesonide on 18 and 29 dpc.

Blood sample collection:

Non-pregnant animals

s.c. at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 hour post dose.

i.v. at pre-dose, 5, 15 min., 1, 2, 4, 6, 8, 10 and 24 hour post dose

Pregnant animals

At pre-dose, 1, 3, 6, 8 and 24 hours post dose

Results

Note: as part of the sample preparation procedure, B9207-015 was converted into B9207-021 by the addition of esterase. Therefore, the measured B9207-021 included both B9207-015 and B9207-021.

Systemic bioavailability of the drug given to rabbits subcutaneously was about 80% in non-pregnant and pregnant rabbits (see details PK parameters in the following table)

Mean values of PK parameters (total of ciclesonide and RM1)

	Nonpregnant			Pregnant, 18 dpc
	50 µg/kg i.v.	25 µg/kg s.c.	100 µg/kg s.c.	100 µg/kg s.c.
AUC _(0-∞) (ng.h/ml)	32.3	12.5	54.3	53.2
C _{max} (ng/ml)		1.6	7.9	5.5
T _{max} (h)	-	1.7	2.3	3.0
T _{1/2} (h)	6.2	5.8	4.9	5.9
F _{systemic} (%)	reference	77	84	82

Measurement of maternal and fetal serum drug concentrations on 29 dpc revealed that fetal drug concentrations were lower than maternal by a factor of about 6 (range: 3.5-10). The table below presents the details.

Animal No	Pregnant rabbit		fetus
	Day 18	Day 29	Day 29
7	7.9	7.9	1.3, 1.2, 1.3
8	8.2	2.0	0.56, 0.48
10	2.6	2.4	0.25, 0.32, 0.37, 0.36
mean±SD	6.2±3.2	4.1±3.3	0.68±0.44

Conclusions: Systemic bioavailability of the drug given to rabbits subcutaneously was as about 80% in non-pregnant and pregnant rabbits. Measurement of maternal and fetal serum drug concentrations on 29 dpc revealed that fetal drug concentrations were lower than maternal by a factor of about 6.

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2.6.4.9 Discussion and Conclusions

Ciclesonide is a pro-drug and it is rapidly de-esterified to active metabolites M1 in lung and circulation. R-epimer instead of S-epimer was developed

Oral bioavailabilities of ciclesonide and RM1 are very low due to the extensive first pass effect. Both ciclesonide and RM1 have a large volume of distribution (4-6 L/kg in rats, mice and dogs). Absorbed ciclesonide and/or RM1 were primarily distributed to lung, heart, thyroid, adrenals, liver, and kidneys. Studies in pregnant and lactating rats demonstrated that this drug and its metabolites do not pass placenta but are secreted into milk in appreciable amount. In vivo RM1 is further metabolized to hippuric acid, 4, 5-dihydro RM1, B-ring-hydroxylated RM1, isomer of dihydroxy RM1 and isomers cyclohexane-hydroxylated RM1, as well as other minor metabolites. There were no qualitative differences in metabolites observed among the species studied. All of the metabolites of RM1 are pharmacologically inactive. In lung, fatty acid conjugates of RM1 was observed and considered as a reservoir of active drug due to the reversible nature of the conjugation and inactive nature of the conjugates. T_{1/2} of ciclesonide was short (1 hour in rats and mice) which is probably due to conversion of ciclesonide to RM1. T_{1/2} of RM1 was 2.4 to 7 hours in rats, mice, rabbits, and dogs. Plasma protein bindings for both ciclesonide and RM1, in animals and humans, were 99%. The primary elimination pathway is bile and feces (80%). The plasma clearances in all animal species

tested were equal or greater than liver blood flow. Exposure to Ciclesonide and/or RM1 does not induce or inhibit liver enzymes.

Toxicokinetics studies showed that, when given by inhalation, systemic exposures to ciclesonide and/or RM1 (AUC) was in proportional to the doses and no drug accumulation over time.

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ON ORIGINAL**

2.6.4.10 Tables and figures to include comparative TK summary

The following table compares PK parameters of ciclesonide and RM1

Species	parameter	Ciclesonide		RM1	
		i.v.	p.o.	i.v.	p.o.
Mouse	Dose (mg/kg)	0.75	0.75	0.75	0.75
	Tmax (hr)	0.083	ND	0.083	0.5
	Cmax (µg/l)	198	ND	109	0.3
	AUC (ng.h/ml)	82	ND	100	1.4
	T _{1/2} (hr)	1	ND	7	2.5
	Vss (L/kg)	5.1	-	-	-
	Abs. Bioavailability	-	-	-	1.4%
Rat	Dose (mg/kg)	0.5	0.5	0.5	0.5
	Tmax (hr)	0.083	ND	0.083	0.083
	Cmax (µg/l)	158	ND	73	0.29
	AUC (ng.h/ml)	64	ND	84	0.8
	T _{1/2} (hr)	1	ND	5	3.4
	Vss (L/kg)	4.2	-	-	-
	Abs. Bioavailability	-	-	-	0.95%
Rabbit	Dose (mg/kg)	0.02	0.1	0.02	0.1
	Tmax (hr)	0.083	ND	0.083	ND
	Cmax (µg/l)	0.64	ND	8.3	ND
	AUC (ng.h/ml)	ND	ND	13.5	ND
	T _{1/2} (hr)	ND	ND	2.4	ND
	Vss (L/kg)	ND	-	-	-
	Abs. Bioavailability	-	-	-	-
Dog	Dose (mg/kg)	0.1	0.5	0.1	0.5
	Tmax (hr)	0.25	0.42	0.38	0.79
	Cmax (µg/l)	121	4	18	3.8
	AUC (ng.h/ml)	36**	81**	29	8.4
	T _{1/2} (hr)	ND	ND	3.3	3.3
	Vss (L/kg)	-	-	-	-
	Abs. Bioavailability	-	-	-	-
Human	Dose (mg/kg)	0.016	0.2	0.016	0.2
	Tmax (hr)	0.17	NA	0.43	3.92
	Cmax (µg/l)	21.91	NA	1.07	0.138
	AUC (ng.h/ml)	5.41	NA	3.17	0.95*
	T _{1/2} (hr)	0.94	NA	2.8	NA

*AUC_{0-12h}; NA=not ascertainable

** unreliable data as the ciclesonide was also detected in all pre-dose samples at an average concentration of 1.243 ng/ml. The source of contamination could not be identified and the levels of ciclesonide were considered undeterminable. The relative ratio of oral versus IV AUC_{0-∞} values of RM1 after oral IV and oral dosing of ciclesonide

was 5.8% and this number (rather than combined ciclesonide and RM1) was considered as oral bioavailability in dogs.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A.

2.6.6 TOXICOLOGY

Note: The doses in the inhalation studies were referred to pulmonary deposited doses assuming 50% deposition factor in rats and dogs, i.e., 50% of delivered dose deposited in the lung. This deposition factor of 50% was used by the Sponsor and previous reviewers in the Division. Based on the current scientific knowledge, pulmonary deposition factor based on the particle sizes used in the studies are 10% in rats and 25% in dogs.

In this review, the inhalation doses (mg/kg) derived from a pulmonary deposition factor of 50% were used for the purpose of identifying treatment group.

2.6.6.1 Overall toxicology summary

General toxicology: The lethal dose of ciclesonide in mice and rats were 200 mg/kg by intraperitoneal administration and greater than 2000 mg/kg by oral administration.

Inhalation exposures of ciclesonide to rats up to 6 months and dogs up to 12 months resulted in typical glucocorticoid effects in a dose and treatment duration dependent manner. These effects were decreases of body weights (or body weight gains), adrenal suppression, and lymphoid tissue atrophy (thymus, spleen and lymph nodes, bronchus-associated lymphoid tissue).

Genetic toxicology:

Ciclesonide was negative in Ames test, chromosome aberration assay in human peripheral lymphocyte, CHO/HGPRT forward mutation assay, and micronucleus test in V79 cells, but was positive in mouse micronucleus test.

Carcinogenicity:

Two-year carcinogenicity studies were conducted in mice by oral gavage at doses of 150, 450 and 900 µg/kg and in rats by inhalation at delivered doses of 30, 76 and 193 µg/kg. Ciclesonide did not increase any tumor incidences in mice and rats.

Reproductive toxicology:

Effects of ciclesonide in fertility and early embryo development were studied using rats. Oral doses (0.1 to 0.9 mg/kg) ciclesonide given to rats (males and females) caused no toxicities in rat fertility, in spite of the effects of reducing body weight gains and food consumption.

Ciclesonide toxicities in embryofetal development were studied in rats and rabbits.

Rats given oral dose of ciclesonide (0.1 to 0.9 mg/kg, during Day 6 to 15 post coitus) were observed with 15% reduction of body weight gains at 0.9 mg/kg, but no toxicologically significant treated-related effects on fetuses.

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.

Special toxicology:

Intravenous treatment of ciclesonide or vehicle (ethanol and polypylene glycol) to dogs resulted in hemolysis in a dosing volume dependent manner. The hemolysis appeared vehicle related. An in vitro rat, rabbit, and dog blood compatibility test resulted in no hemolysis (drug concentration: 2.1 µg/ml) and the order of erythrocyte stability was as follows: human>dogs>rats.

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.

Rats receiving ciclesonide at 16.4-163 µg/kg by inhalation had no changes in ACTH or sex related hormones (testosterone, estradiol, progesterone, luternizing hormone, follicle stimulating hormone, adrenocortical hormone and prolactin) in spite of findings of decrease of body weights or body weight loss (4% compared to Day 0), and decreases of corticosterone (47-52% at HD).

2.6.6.2 Single-dose toxicity

Acute single dose toxicity studies in mice and rats were conducted by intraperitoneal injection (50, 100 and 200 mg/kg) and oral gavage (2000 mg/kg). Histopathology examinations were not performed in these studies. Mortalities of 1/5 per sex at intraperitoneal dose of 200 mg/kg were observed in both mouse and rat studies. No mortalities occurred in the mice or rats receiving oral dose of 2000 mg/kg. The minimum lethal doses in mice and rats were 200 mg/kg by intraperitoneal treatment and were greater than 2000 mg/kg by oral treatment. See details of these studies in Attachment 1.

2.6.6.3 Repeat-dose toxicity

Rat toxicity studies for 4 weeks and 6 months were conducted each with administration routes of inhalation, oral and subcutaneous administrations. Dog studies were conducted with administration routes of inhalation (4 weeks, 3 months, 6 months, and 12 months), oral (4 weeks and 12 months) and intravenous infusion (2weeks). Similar drug toxicities were observed in studies with different routes of administration. Major toxicities findings were typical for glucocorticoids including decreases of body weights (or body weight gains), adrenal suppression manifested as decreased adrenal weight and microscopic cortical atrophy, lymphoid tissue atrophy (thymus, spleen and lymph nodes). Additionally, mammary glandular development and interstitial mononuclear cell infiltration in lungs was seen in the 6-month rat inhalation study. Skin hair follicle regression, ovary atrophy and thickened lung alveolar septa were seen in the 12-month dog inhalation study. All of the toxicity findings were dose related. The following table summarizes the NOAELs defined in inhalation studies.

Species, strain	Dosing formula	Dosing Duration	Doses (µg/kg)	NOAEL (µg/kg)	Study #
Rat, SD	Dry powder	4 weeks	15.3, 50.5, 156.5	50.5	121E/94
Rat, Wistar	MDI	4 weeks	18, 53, 164	53	92E/97
Rat, SD	Dry powder	6 months	16.5, 47, 167	16.5*	138E/95K1
Dog, beagle	Dry powder	4 weeks	15, 50, 100	σ, 50; ♀, 15	205/94
Dog, beagle	MDI	4 weeks	19, 61, 118	61	103/97
Dog, beagle	MDI vs DPI	3 months	15, 53, 111/113 (MDI/DPI)	15	273/98
Dog, beagle	Dry powder	12 months	18, 47, 92	18**	116/96

Note: the NOAELs in this table are defined by the Division and the values of the NOAELs refer to pulmonary deposited doses using 50% deposition factor. Currently, pulmonary deposition factor of 10% in rats and 25% in dogs are used. However, 50% of deposition factor has been used by the sponsor and previous reviewer in the Division. For the purpose of identifying treatment groups and avoid confusion, correct NOAELs values are not listed.

For details of each study, see attachment 1, 2, 3, 4, 5, and 7 (IND 53391, Study 92E/97 and 112E/94 in review #2 on 11/05/1997; Study 138E/95 and 205/94 in Review #1 on 08/01/1997; Study 103/97 in Review #3 on 11/05/1997, Study 273/98 in Review # 8 on 12/07/2001 and Study 116/96 in Reviews # 1, 4, 6).

*Initially the rat 6-month study was considered no NOAEL defined due to the incidence of multifocal histiocytosis in the lungs. Evaluation by peer pathologist showed histiocytosis of "slight" grade not to be significant. The dose of 16.5 µg/kg was accepted as the NOALE (see Review 4 for IND 53391, Attachment 4).

**The dogs in the 12-month study were also observed with additional toxicities which resulted in no NOAEL defined initially. These toxicities were chondrosis, osteofibrosis, and osseous disorganization of the maxilloturbinates of nasal cavity, and spermiogenic disturbance. The findings of spermiogenic disturbance were also reported in a 3-month dog study. For the nasal trabecular findings, the sponsor provided background data from ciclesonide and two other drugs with a blinded re-reading of nasal cavity histological slides. Additionally, in response to the Division's recommendation, the sponsor provided a dog 12-month oral study report. Upon evaluation of these data, the Division agreed that nasal trabecular changes were background findings in dogs (Attachment 5). For spermiogenic disturbance, in response to the Division's concern, the Sponsor explained that the findings represent an artifact of processing, and provided a re-evaluation of the slides by Pathology Working Group. The Division considered this finding represents a very low level of concern regarding possible risk to human subjects. This conclusion was based on several factors, including the absence of cellular injury, and the findings of the external expert panel. Details of the studies and communications with the sponsor concerning the issue of spermiogenic disturbance are in Attachment 1, 7, 8, and 9.

2.6.6.4 Genetic toxicology

Ciclesonide has been tested for genotoxicity in Ames test, chromosome aberration assay in human peripheral lymphocyte, CHO/HGPRT forward mutation assay, micronucleus test in V79 cells, and mouse micronucleus test. The positive findings were observed in mouse micronucleus test only (See details in attachment 1).

2.6.6.5 Carcinogenicity

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. See details in Attachment 10.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Oral treatment of rats (males, -4 weeks to up to 3 weeks of mating period, females, -14 days to day 14 post coitum) with ciclesonide (0.1 to 0.9 mg/kg) showed no toxicity for fertility, in spite of the effects of reducing body weight gains and food consumption. See details in Attachment 6.

Embryofetal development

Ciclesonide toxicities in embryofetal development were studied in rats and rabbits. Rats given oral dose of ciclesonide (100, 300 and 900 µg/kg, during Day 6 to 15 post coitus) were observed with 15% reduction of body weight gains at 900 µg/kg, but no toxicologically significant treated-related effects on fetuses (see details in Attachment 1).

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 100 $\mu\text{g}/\text{kg}$ and above. There were no living fetuses in HD group. Fetal weight was reduced at 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 25 $\mu\text{g}/\text{kg}$ and above and embryocidal at 100 $\mu\text{g}/\text{kg}$ and above. Details of this study are presented in the original review for IND 53391 in Attachment 1.

In order to define the NOAEL, a rabbit study with lower doses was conducted. The following is the review for this study.

**APPEARS THIS WAY
ON ORIGINAL**

Toxicity of B9207-015 for reproduction. Study for effects on embryo-fetal development in the rabbit after subcutaneous administration

Background: A previous review on a teratogenicity study in rabbits (subcutaneously at doses of 25, 100 and 400 µg/kg) reported teratogenic and fetotoxic effects of the test drug at 25 µg/kg and above (Attachment 1). In the end of phase II meeting, the Division recommended to lower doses in rabbit embryo-fetal development study to define NOAEL.

Key study findings: The doses used in this Segment II study did not induced maternal toxicities but fetal toxicities of acampsia and cleft palate were observed. The low dose of 1 µg/kg was considered NOAEL.

Research report #: 283/99

Study /protocol #: Byk Gulden study TK0647

Volume #: 2.6.7.13.

Conducting Lab. and location: Byk Gulden Institute of Pathology and Toxicology, Germany

Study period: 08/12/1999 -09/06/1999.

GLP compliance: Yes.

Quality assurance: Yes.

Drug, lot # and purity: Ciclesonide, Batch No. MG225/C, 98.1% purity.

Methods

Doses: 1, 5 and 25 µg/kg

Species/strain: "Little Russians" Rabbits

Number/sex/group: 16 females/dose

Route, formulation, volume, and infusion rate: Subcutaneously administered as a solution in PEG 400 in the volume of 0.2 ml/kg

Satellite groups used for toxicokinetics: Not conducted.

Study design: The female rabbits were given the test drug for 13 days (6-18 dpc= days post coitum) and autopsied on day 29 post coitum.

Parameters and endpoints evaluated:

Dams: Clinical signs and mortality were observed daily. Body weights were measured on 0 dpc, and from 6 dpc until autopsy daily. Food consumptions were measured daily. Autopsy of dams were conducted on 29 dpc, gravid uterus weights, number of implantations, number of living fetuses/dam and placenta weights, corpora lutea number, and data of pre-implantation loss and post-implantation loss were obtained.

Fetuses: Appearance, behavior, body weights, quotient of female:male fetuses, fetal morphology, external (including oral cavity) and visceral changes (thoracic, abdominal and cranial cavities), head and skeletal changes were recorded. Severe malformed fetuses were examined for

external changes only. Organs under suspicion were examined for histopathology.

Results

Mortality (dams): All animals were sacrificed at term.

Clinical signs (dams): No drug-related findings

Body weight (dams): No drug-related findings

Food consumption (dams): No drug-related findings

Autopsy

Gravid uterus weights: No drug-related findings

Number of implantations: There were no differences between groups.

Living fetuses: The number of fetuses was similar in all groups.

Placental weights: No remarkable findings

Number of corpora lutea: No remarkable findings

Pre- and post-implantation loss: No remarkable findings

Toxicokinetics: Not performed

Offspring (malformations, variations, etc.):

Behavior and appearance: No remarkable findings

Body weights: Fetal weights per litter were decreased in a dose-related manner as detailed in the table below.

Dose ($\mu\text{g}/\text{kg}$)	0	1	5	25
Number of Pregnancies	16	16	16	16
Live fetuses	103	99	111	106
$\sigma/\text{♀}$	56/47	44/55	44/67	45/61
mean fetal wt/litter(g)	36.7	38.1	35.6	33.2*

* $P < 0.005$ compared to control.

Sex ratio: No drug-related effects were observed.

Fetal morphology:

The abnormalities in the fetal morphology were cleft palate, acampsias (flexures of legs), and dose-related increased incidence of incomplete ossification of bones (temporal, pubic, parietal, talus). These findings have been reported previously (25 $\mu\text{g}/\text{kg}$: cleft palate 2/77 fetuses, acampsias 3/77 fetuses; 100 $\mu\text{g}/\text{kg}$, cleft palate 22/45 fetuses, acampsia 37/45 fetuses). See Attachment 1 for study #106/95 review. In the current report, the sponsor indicated that acampsia (flexures of the forelegs) is a well known finding in this strain of rabbit but the incidence in the 5 $\mu\text{g}/\text{kg}$ group was higher than usual (no historical data provided).

The findings of one chamber heart and missing testis and epididymis at the high dose group were not observed in the previous study (Study 106/95) using higher doses and were considered incidental findings. The findings only in one litter of mid dose group including antetorsion, diaphragm without muscle, ascites, asplenia, and enlarged fontanelle were not considered drug-related. The following table presents the incidence of morphological abnormalities in this study.

Dose ($\mu\text{g}/\text{kg}$)	0	1	5	25
No. Litters Evaluated	16	16	16	16
No. Live fetuses	103	99	111	106
Defects (n fetus/n Litter)				
Cleft palate				1/1
Microglossias			4/1	
Flexure of foreleg		1/1	7/3	1/1
Flexure of hindleg			3/1	
Antetorsion			3/1	
Diaphragm without muscle			4/1	
Ascites			1/1	
Asplenia			1/1	
One chamber heart				1/1
Missing testis and epididymis				1/1
Enlarged fontanelle			1/1	
Incomplete ossification of				
pubic bone	1/1	2/1	11/8	18/10
frontal bone	18/10	23/12	34/14	43/15
parietal bone	18/12	19/11	26/13	39/16
temporal bone	9/6	10/6	12/8	24/10
talus	1/1		6/5	10/6

Note: In one litter of the 5 mg/kg group, 4 of 8 fetuses were revealed the following findings: 4 flexures of the foreleg, 3 flexures of the hindleg, 1 antetorsin of the hindleg, 4 microglossias, 4 diaphragm without muscle, and some minor changes including thickened ischial bone, crooked scapula, and enlarged spina scapula.

Conclusions:

In this rabbit teratogenicity study, ciclesonide administered subcutaneously at doses of 1, 5 and 25 $\mu\text{g}/\text{kg}$ caused no maternal toxicities. Fetal toxicity findings were slight decrease of fetal body weights, flexure of legs, cleft palate. The findings of flexures of legs and cleft palate in the current study were considered drug-related based on the similar findings and dose relationship reported in the previous study. The dose of 1 $\mu\text{g}/\text{kg}$ was defined as the NOAEL based on the findings of flexure of legs in the next higher dose level. The sponsor concluded the same NOAEL for this study.

Prenatal and postnatal development

Ciclesonide: Study for effects on pre- and postnatal development including maternal function in the rat

Key study findings: female rats given oral ciclesonide at 0.1 to 0.9 mg/kg from Day 6 post coitum to Day 20 post partum were observed with decrease of F0 maternal body weight gain and F1 body weights in the first 21 days post partum. There were no drug-related findings in F0 female reproduction, breeding and autopsy. There were no abnormalities in F1 physical development, behavior and reproduction. There were no abnormalities in F2 as examined on external appearances, sex ratio and body weights.

Study report no.: 235/00

Study/protocol no. 734376

Volume #, and page #: eNDA, 2.6.7.14

Conducting laboratory and location: _____

b(4)

Study period: 07/23/1999 – 09/11/2000

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: Ciclesonide batch MS 470/C, purity 99.15%

Methods

Doses: 0, 0.1, 0.3, 0.9 mg/kg, 7x/week.

Species/strain: Rats, Wistar

Number/sex/group: 24 females/group

Route, formulation, volume, and infusion rate: Gavage, administered as a solution in PEG 400, volume 4 ml/kg, controls received PEG 400.

Satellite groups used for toxicokinetics: None

Study design: Female rats were given the test drug from Day 6 post coitum to day 20 post partum (p.p.). Autopsies were conducted for F0 parent females on day 21 post partum, F1 parent females on day 21 post coitum, F1 parent males after caesarian section of F1 parent females.

Parameters and endpoints evaluated:

- Mortality and clinical signs (F0 and F1): twice daily.
- Body weights: F0 Dams, daily; F1 dams, on Days 0, 6, 11, 14 and 21 post coitum.
- Food consumptions: F0 dams, on days 0-6, 11-15, 15-21 post coitum and days 0-4, 4-7 and 7-14 of the lactation period; F1 dams were not recorded.
- Postnatal observations (F0 dams and F1 pups):
 - F0 Dams: Nesting and nursing behavior of the dams were observed. Autopsy was conducted on day 21 p.p. and structural abnormalities, pathological changes and hemorrhagic areas of implantation sites were recorded.

F1 offspring at birth and during lactation: 1). Duration of gestation, 2). Sex of pups and number of newborns with external abnormalities including oral cavity, 3). Number of live and dead pups after parturition and on days 1, 4, 7, 14 and 21 lactation, 4). Individual pup weights and mean body weights by sex on days 1, 4, 7, 14, 21 and 35 post partum.

Physical development and behavioral tests for F1:

Pinna unfolding (2-6 p.p.)
Incisor eruption (6-11 p.p.)
Onset of coat development (8-15 p.p.)
Eye opening (13-20 p.p.)
Testes descent (21-28 p.p.)
Cleavage of balanopreputial gland (25-34 p.p.)
Vaginal opening (30-43 p.p.)
Right reflex (14 p.p.)
Photophobotaxis (21±1p.p.)
Cliff avoidance (21 p.p.)
Palmar grasp ability (16±1p.p.)
Negative geotaxis on slope 45° (21±1p.p.)
Exploratory locomotor pattern in a cylindrical cage (21 p.p.)
Direct papillary reflex (21±1p.p.)
Hearing ability (21±1p.p.)
Water maze tests according Hummler for three different tests:
learning, memory and relearning tests (36-43±1p.p.)

After weaning on Day 21, 24 F1 rats per sex from each of dose level (refer to the dose of F0 dams) were randomly selected for F1 reproductive performance evaluation.

Reproductive performance of the F1:

F1 animals were paired when they were at least 10 weeks old.
Siblings were not paired.
Estrus cycles determination: From 2 weeks prior to pairing to day 0 post coitum.

Post mortem examination for F1 dams: On 21 dpc, F1 dams were macroscopically examined for all internal organs, with emphasis on uterus, uterine contents, position of fetuses in the uterus and number of corpora lutea. The uteri (and contents) of all females with live fetuses were weighted at necropsy on 21 dpc. The fetuses were weighted, examined for gross external abnormalities.

F1 offspring: Sacrificed and examined macroscopically during week 8 post partum. Body weights and organ weights of pituitary,

adrenals, thyroid, testes, epididymides, ovaries and uterus were obtained.

F1 parent males: Macroscopic examinations were performed after Caecarean section of the F1 parent females.

Organs/tissues preserved: Organs/tissues with gross lesions of all animals and F1 pups with external abnormalities and which died during the study.

Results

F₀ in-life:

Mortality and clinical signs:

All dams survived until scheduled necropsy. Soft feces was seen in all groups and was considered vehicle polyethylene glycol related.

Food consumption:

During the gestation period (6-21 dpc), HD group had 7% reduction of food consumption than vehicle control.

During lactation period, HD group had 13% and 7% decrease of food consumptions during Days 1-4 and Days 4-7 lactation period, respectively. There was no difference between HD and control during Days 7-14 of lactation period. For the entire lactation period, mean food consumption amongst control and LD and MD was similar.

Body weights:

During gestation period (6-21 dpc), body weight gain decreased 3.3%, 10% and 21% relative to vehicle control in LD, MD and HD, respectively.

During lactation period, there were no drug related body weight gain differences amongst all 4 groups.

Maternal reproduction data and indices of breeding data:

With the exception of two non-pregnant females in MD group, all mated females were pregnant and gave birth and reared their pups up to day 21 post partum.

Maternal pregnancy parameters were similar for all of the 4 groups including duration of gestation, implantations per dam, post implantation loss, dead pups at first litter check, living pup at first litter check, postnatal loss (days 0-4 p.p.), breeding loss (days 5-21 p.p.), living pups on days 21 p.p., birth index (% of pups born alive in the number of implantations), viability index (% alive pups in days 4 p.p. in pups born alive), and weaning index (% of alive pups on day 21 p.p. in alive pups on day 4 p.p.).

F₀ necropsy:

There were no abnormal macroscopic changes in any female of any group.

F₁ physical development:

Abnormalities in first check: None.

Sex ratio of pups: Similar in all groups.

Body weights of F1:

Body weights lower 5.8-11.7% than control within first 21 days post partum and a tendency of decrease body weights during the first 7 post partum were seen in HD and MD groups, respectively. After weaning until day 35 post partum, body weight gains were similar in control, LD and MD groups and slightly lower in HD group.

Developmental indices and findings during lactation and rearing period:

There were no test drug related changes in the developmental indices other than marginally delayed testicular descent (control, 23.0; LD, 23.8; MD, 23.7; HD, 24.1 days p.p.) and slightly delayed preputial opening (control, 29.9; LD, 30.8; MD, 31.1; HD, 30.7 days p. p.). There were no abnormal findings attributable to treatment in the F1 during the lactation and rearing periods (days 0-35 post partum). There were no drug related findings in necropsy examination.

F₁ behavioral evaluation:

There were no drug-related effects noted. Slightly lower in activity test for drug treated animals were not biological significant (control, 2.3; LD, 2.2; MD, 2.1; HD, 2.0 on the scale of 4 based on the following criteria: 0=activity, 1=exploratory behavior, 2=rearing against wall, 3=trying to escape).

F₁ reproduction:

There were no differences noted amongst all groups in estrus cycles, parental reproduction parameters (precital time, percentage mating, fertility index, conception rate), and maternal reproduction data including number of corpora lutea, pre-implantation loss, number of implantation sites, and number of fetuses per dam. The higher post-implantation losses in MD (12.1%) and HD (8.3%) than control (3.6%) were not considered drug-related because of a lack of dose dependency and were within historical control range.

F₂ findings:

There were no remarkable findings in external examinations, sex ratio, and body weights.

Conclusions:

Female rats given ciclesonide at doses of 0.1, 0.3 and 0.9 mg/kg by gavage from Day 6 post coitum to Day 20 post partum resulted in decreases of F0 maternal body weight gain (up to 21%) during gestation and decreases F1 body weights up to 11.7% in the first 21 days post partum. Decreases of food consumptions were seen in F0 females during gestation and first 7 days of lactation period. There were no drug-related findings in F0 females in reproduction, breeding and autopsy. Studies in F1 physical development,

behavior and reproduction revealed no drug related findings. F2 generation was not affected (by the drug exposures to F0) as examined on external appearances, sex ratio and body weights.

2.6.6.7 Local tolerance

Epicutaneous administration with ciclesonide resulted in no sign of irritation in guinea pigs. Rabbits received ciclesonide or vehicle (propylene glycol) by i.v., paravenous, or intra-arterial route were observed with necrotizing inflammations or vasculitis. Thus the positive findings were confounded with the effect of the vehicle. See details in Attachment #2.

2.6.6.8 Special toxicology studies

Intravenous treatment of ciclesonide or vehicle (ethanol and polypropylene glycol) to dogs resulted in hemolysis in a dosing volume dependent manner. The hemolysis appeared vehicle related. An in vitro rat, rabbit, and dog blood compatibility test resulted in no hemolysis (drug concentration: 2.1 µg/ml) and the order of erythrocyte stability was as follows: human>dogs>rats. Details can be found in Attachment 2.

Active systemic anaphylaxis and passive cutaneous anaphylaxis tested in guinea pigs and mice-rats passive cutaneous anaphylaxis test for ciclesonide showed negative results. See details in Attachment 7.

A study for endocrine toxicity of ciclesonide in rats was reported in the current submission and reviewed as follows. This study demonstrated that ciclesonide treatment does not affect sex related hormone levels.

Study title: 28-Day Toxicity Study in Rats Treated with B9207-015 by inhalation

Key study findings: Inhalation of ciclesonide at doses up to 163 µg/kg did not affect sex hormone levels in rats.

Study no.: 59/2001

Volume #, and page #: eNDA 2.6.7

Conducting laboratory and location: _____

b(4)

Date of study initiation: 07/12/2000

GLP compliance: The report was accompanied with a GLP compliance statement.

QA reports: yes (X) no ()

Drug, lot #, and % purity: Ciclesonide (B9207-015) batch 4BG005 (MDI with ethanol HFA134a), maximum total impurity ~ %.

Formulation/vehicle: Ethanol ~ %

Methods

Wistar rats (10 males and 40 females per dose) were exposed to ciclesonide by nose-only inhalation 1h/day at 1 or 10 mg/m³ aerosol concentrations for 28 days.

All animals were observed daily and animals' body weights were recorded starting on Day -7. Necropsy was conducted at termination.

Blood was collected for hormone determination that included testosterone, estradiol, progesterone, luteinizing hormone, corticosterone, follicle stimulating hormone, adrenocortical hormone and prolactin. Organs examined for evaluation of estrus cycle and histopathological examinations were ovaries, uterus and vagina.

Results:

The calculated pulmonary deposited dose of B9207-015, assuming 50% deposition factor, for males/females was average of 16.4 $\mu\text{g}/\text{kg}/\text{day}$ in the 1 mg/m^3 group, and 163 $\mu\text{g}/\text{kg}/\text{day}$ in the 10.0 mg/m^3 group.

Body weight gains in treated groups were dose-dependent (males, HD, $\downarrow$ 76%; females: LD, $\downarrow$ 38%; HD, body weight loss 4% compared to that on Day 0)

Corticosterone (CCN) was decreased 52% in HD males and 47% in HD females. There were no significant alteration in ACTH or sex hormones were observed. There were no estrus cycle related hormone changes observed in proestus, estrus or metestus phases.

Conclusion:

Ciclesonide had no impact on sex hormone levels at the doses up to 163 $\mu\text{g}/\text{kg}$ by inhalation for 28 days although decreased body weights and/or body weight gains and decreased plasma corticosterone concentrations were observed.

2.6.6.9 Discussion and Conclusions

Single dose studies revealed that lethal doses of ciclesonide in mice and rats were 200 mg/kg by intraperitoneal administration and greater than 2000 mg/kg by oral administration. Repeat dose inhalation studies with dosing durations up to 6 months in rats and 12 months in dogs were observed with typical glucocorticoid effects in a dose and duration related manner. These effects included decreases of body weights (or body weight gains), adrenal suppression, and lymphoid tissue atrophy (thymus, spleen and lymph nodes, bronchus-associated lymphoid tissue). Additionally mammary glandular development in rat 6 month study, and hair follicle regression and thickened alveolar septa in 12 month dog study were observed.

A series of genotoxicity studies were performed and negative results were obtained in all of the studies except mouse micronucleus test which was positive. Two-Year carcinogenicity studies in mice and rats demonstrated that this drug does not induce or increase any tumor incidences.

In reproductive toxicity aspect, as tested in rats, ciclesonide does not cause toxicities to fertility and early embryonic development, embryofetal development, or prenatal and postnatal development. However, this drug was teratogenic in rabbits at subcutaneous doses of 5 $\mu\text{g}/\text{kg}$ and above and was embryocidal at 100 $\mu\text{g}/\text{kg}$ and above. Thus a pregnancy category C for this drug in labeling is appropriate.

Additionally, local tolerance test in guinea pigs failed to exclude vehicle effects of irritation. However, no local irritation was reported in general toxicology studies,

therefore, this drug is not considered a local irritant. Ciclesonide does not have hemolytic effects tested in vitro in rat, rabbit and dog blood. Anaphylactic tests in guinea pigs and rat-mice cutaneous anaphylaxis studies revealed that this drug is not an anaphylactic agent.

Effects of ciclesonide on endocrine system were studied in rats. Treatment of ciclesonide at doses up to 163 µg/kg (pulmonary deposited doses based on deposition factor of 50%) for 28 days were observed with decreases of body weights and plasma cortocosterone levels, but not changes in sex hormone levels (testosterone, estradiol, progesterone, luterinzing hormone and prolactin) or estrus cycles.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

Study type	Species	Route	Dose	Remarkable findings	NOAEL
Acute Tox	mouse	oral	2000 mg/kg	Not observed	Lethal dose>2000 mg/kg
Acute Tox	mouse	I.P.	50, 100, 200 mg/kg	mortality, ↓ body wt and food consumption, atrophy of thymus, spleen a adrenal gland	Lethal dose =200 mg/kg
Acute Tox	rat	oral	2000 mg/kg	Body wt decrease, adrenal and splenic atrophy	Lethal dose >2000 mg/kg
Acute Tox	rat	I.P.	50, 100, 200 mg/kg	Mortality, ↓ body wt and food consumption, atrophy of thymus, spleen and lung histiocytosis	Lethal dose =200 mg/kg
4-week Tox	rat	I.H.	15, 51, 156 µg/kg	↓ body wt and food consumption, lymphoid depletion in thymus	51 µg/kg
4-week Tox	rat	I.H.	18, 53, 164 µg/kg	↓ body wt and food consumption, lymphoid depletion in thymus and spleen	53 µg/kg
6-month Tox	rat	I.H.	17, 48, 166 µg/kg	↓ body wt and food consumption, ↓WBC and lymphocyte count, lymphoid atrophy/depletion in BALT, mesenteric LN, and thymus. Mammary glandular development.	17 µg/kg
4-week Tox	dog	I.H.	19, 61, 118 µg/kg	Lymphoid atrophy in thymus, spleen, and lymph nodes, and adrenal atrophy	61 µg/kg
3-month Tox	dog	I.H.	15, 53, 111, 113 µg/kg	Adrenal atrophy, lymphoid atrophy (thymus, spleen, lymph nodes)	15 µg/kg
1-year Tox	dog	I.H.	18, 47, 92 µg/kg	Lymphoid atrophy (thymus, lymph nodes), adrenal atrophy, skin hair follicle regression, ovary atrophy	18 µg/kg
2-year Car.	rat	I.H.	30, 76, 193 µg/kg	Typical glucocorticoid effects, but no induction or increase of tumor incidence	NA

2-year Car.	mouse	oral	150, 450, 900 µg/kg	no induction or increase of tumor incidence	NA
Repro. seg I	rat	oral	100, 300, 900 µg/kg	No effects on fertility	900 µg/kg
Repro. Seg II	rat	oral	100, 300, 900 µg/kg	No effects on embryo-fetal development	900 µg/kg
Repro. Seg II	rabbit	S.C.	25, 100, 400 µg/kg	Post-implantation loss, reduced litter weights, cleft palates, acampsias, largeness of fontanelle, excephaly, pergameneous skin.	No NOAEL
Repro. Seg II	rabbit	S.C.	1, 5, 25 µg/kg	Acampsias and cleft palate	1 µg/kg
Repro. Seg III	rat	oral	100, 300, 900 µg/kg	No drug related findings in F0 reproduction, breeding, and autopsy, in F1 physical development, behavior and reproduction, in F2 external appearance sex ratio and body weights.	900 µg/kg
Genotox in vitro	Chrom. ab. in human Lφ.			negative	
	CHO/HGPRT mutation in V79 cells			negative	NA
	Micronucleus test in V79 cells			negative	NA
Genotox in vivo	Mouse micronucleus test			positive	NA
Special tox	Effects on sex hormone in rats given 4-week IH doses up to 163 µg/kg			Ciclesonide had no impact on sex hormones although decrease of corticosterone was seen.	NA

Note: doses and NOAELs in the inhalation toxicity studies were derived from inhalable dose and pulmonary deposition factor of 0.5.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Ciclesonide is a glucocorticoid drug and it exerts its effect primarily through its active metabolite RM1. RM1 has 120-fold higher binding affinity for glucocorticoid receptors than ciclesonide. Ciclesonide and RM1 inhibited lymphocyte proliferation and cytokine release. In animal inflammatory models, ciclesonide and RM1 inhibited inflammatory responses. Additionally, ciclesonide inhibited allergen induced airway hypersensitiveness.

Safety pharmacology studies revealed that ciclesonide has no remarkable effects on neurological, cardiovascular and pulmonary functions.

Oral absorption is high but oral bioavailability for ciclesonide was very low (less than 6% for combined ciclesonide and RM1) due to first pass effect. Ciclesonide was rapidly converted to RM1 by hydrolysis and the RM1 was further metabolized to several other products. All metabolites of RM1 are pharmacologically inactive. Inactive fatty acid ester conjugates of des-ciclesonide were detected in cultures with lung slices and were considered a reversible depot in lung when drug is given by inhalation. Cyp 3A4 was the major enzyme involved in metabolism of RM1. There were no enzyme induction or inhibition observed by exposure to ciclesonide or RM1. Elimination is primarily through

feces (80%). Both ciclesonide and RM1 had 99% of plasma binding in all species examined. T1/2 of RM1 was in the range of 2.4-7 hours in animals.

The lethal dose of ciclesonide in mice and rats were 200 mg/kg by intraperitoneal administration and greater than 2000 mg/kg by oral administration. Animals receiving repeat dose ciclesonide inhalation showed typical glucocorticoid effects in a dose and treatment duration dependent manner. These effects were decreases of body weights (or body weight gains), adrenal suppression, and lymphoid tissue atrophy (thymus, spleen and lymph nodes, bronchus-associated lymphoid tissue).

Ciclesonide was tested negative in the most genotoxicity studies but positive in a mouse micronucleus assay. Two-Year carcinogenicity studies in mice and rats demonstrated that this drug does not induce or increase any tumor incidences.

In reproductive toxicity aspect, in rats, ciclesonide does not have toxicities to fertility and early embryonic development, embryofetal development, or prenatal and postnatal development. However, this drug was teratogenic in rabbits at subcutaneous doses of 5 µg/kg and above and was embryocidal at 100 µg/kg and above. The NOALE was 1 µg/kg in rabbits.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues. All previous unresolved issues (not defined NOALEs in the 6 month rat study due to lung histiocytosis and in 12 month dog study due to the findings in nasal cavity and spermiogenic disturbances have been resolved).

Recommendations:

Ciclesonide inhalation aerosol is recommended to be approved from a preclinical perspective. Toxicities of this drug including general toxicities, genotoxicity in mouse micronucleus test and teratogenic effects in rabbits should be included in the labeling.

Suggested labeling:

Modification of wording is recommended for the information pertaining mechanism of action, genotoxicity, teratogenic effect, and milk secretion of the drug. Based on Medical Officers' recommendation, patients at age of 11 and under are not going to be approved to use this drug. Ratios of animal and human doses regarding to carcinogenicity and overdose information, are included for adults only.

CLINICAL PHARMACOLOGY

Mechanism of Action:

b(4)

b(5)

3 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

ATTACHMENT 1.

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original, Review No. 1

IND Number: 53,391

Serial Number(s): 000

Date(s) of Submission: Letter Date: May 23, 1997
CDER Stamp: June 03, 1997

Information to be Conveyed to Sponsor: Yes (X), No ()

Reviewer: Satish C. Tripathi, Ph.D.

Date Review Completed: August 01, 1997

Sponsor: Byk Gulden Lomberg Chemische Fabrik
GmbH, Postfach 10 03 10, 78403
Konstanz, Germany (Dr. Petra
Willersinn-Kern:
Tel: 011-49-7531-84-2837).

Sponsor (U.S. Representative): Altana Inc., 60 Baylis Road, Melville,
NY 11747 (Miss Virginia Carman:
516-454-7677 Extension 2091).

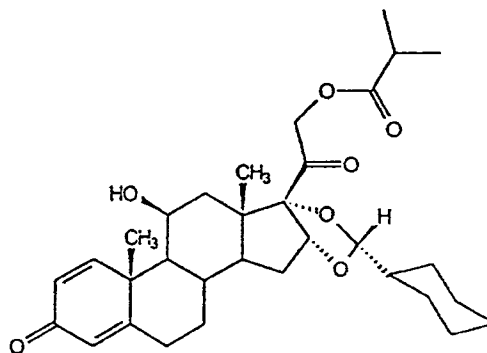
Manufacturer: _____ **b(4)**

Drug Name: Primary: Ciclesonide
Other Names: Byk Gulden B9207-015

Chemical Name: [11 β , 16 α (R)]-16, 17-
[Cyclohexylmethylene) bis(oxy)-11-
hydroxy-21-(2-methyl-1-
oxopropoxy)pregna-1, 4-diene-3, 20-
dione.

CAS Number: 141845-82-1

Structure:



Molecular Weight and Formula: 540.7; C₃₂H₄₄O₇

Related INDs/NDAs/DMFs: DMF ←. Toxicology testing of HFA-134a (MDI Propellant): **b(4)**

Class: Glucocorticoid Steroid.

Indication: Mild to moderate chronic asthma.

Clinical Formulation: White to off-white powder available as MDI that delivers ~, 100, and 200 µg (ex valve) per puff. Other ingredients: ~% (w/w) propellant HFA-134a and ~% (w/w) ethanol. **b(4)**

Route of Administration: Inhalation (via MDI).

Proposed Clinical Protocol:

Objective: To study: (i) the effect of two doses of Ciclesonide vs. placebo on pulmonary function, asthma symptoms, and concomitant use of the β_2 -agonist (albuterol) in patients with chronic asthma; (ii) the long-term safety of Ciclesonide; and (iii) the long-term effect of Ciclesonide on pulmonary function and number of exacerbations.

Dose:

Double-blind segment: 200 or 800 $\mu\text{g}/\text{day}$ (4 Puffs @ 50 or 200 $\mu\text{g}/\text{puff}$).

Open label extension:

Patients without asthma exacerbation: 800 $\mu\text{g}/\text{day}$ (4 puffs once daily)

Patients with asthma exacerbation: 800 $\mu\text{g}/\text{day}$ (4 puffs once daily) or 1600 $\mu\text{g}/\text{day}$ (4 puffs twice daily).

Later phase of open label extension:

200 $\mu\text{g}/\text{day}$ (1 puff @ 200 $\mu\text{g}/\text{puff}$); 400 $\mu\text{g}/\text{day}$ (2 puffs @ 200 $\mu\text{g}/\text{puff}$), 800 $\mu\text{g}/\text{day}$ (4 Puffs @ 200 $\mu\text{g}/\text{puff}$) or 1600 $\mu\text{g}/\text{day}$ (4 Puffs @ 200 $\mu\text{g}/\text{puff}$, bid). For a 50 kg individual, the highest dose translates to 16 $\mu\text{g}/\text{kg}/\text{day}$ (3 months) to 32 $\mu\text{g}/\text{kg}/\text{day}$ (9 months).

Frequency: Daily.

Duration: 12 weeks for double blind segment; 40 weeks for open label.

Patient population: 240 patients (age: 18-70 years; either sex) with chronic asthma.

Previous Review(s), Date(s) and Reviewer(s): None.

Studies Reviewed in this IND:

PHARMACOLOGY
Pharmacodynamics <i>in vivo</i> and <i>in vitro</i> ; Safety Pharmacology; Vol. C2.1
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION
Absorption, distribution, metabolism in rats and dogs, Vol. C2.2-C2.4
TOXICOLOGY
1. Mice: Acute Toxicity (i.p.), Vol. C2.5. 2. Mice: Acute Toxicity (p.o.), Vol. C2.5. 3. Rat: Acute Toxicity (i.p.), Vol. C2.5. 4. Rat: Acute Toxicity (p.o.), Vol. C2.5. 5. Rat: 4-wk Inhalation Toxicity with Dry Powder Formulation, Vol. C2.8. 6. Rat: 4-wk Dose Ranging Inhalation Toxicity with Metered-dose HFA-formulation Vol., C2.8. 7. Rat: 26-wk Inhalation Toxicity with Dry Powder Formulation, Vol. C2.10. 8. Dog: 4-wk Inhalation Toxicity with Dry Powder Formulation, Vol. C2.9. 9. Dog: 52-wk Inhalation Toxicity with Dry Powder Formulation, Vol. C2.12. 10. Dog: 4-wk Inhalation Toxicity with Metered-dose CFC-formulation, Vol. C2.13. 11. Dog: 26-wk Inhalation Toxicity with Metered-dose CFC-formulation, Vol. C2.13.
REPRODUCTIVE TOXICITY
1. Rat: Segment II, Vol. C2.14. 2. Rabbit: Segment II, Vol. C2.14.
GENETIC TOXICITY
<i>In Vitro</i> tests: 1. Bacterial Reverse Mutation (Ames) test, Vol. C2.13. 2. Chromosomal aberration in human lymphocytes, Vol. C2.13. 3. HPRT test (V79 cells) , Vol. C2.14. 4. Micronucleus test with V79 cells, Vol. C2.14. <i>In Vivo</i> tests: 1. Mouse micronucleus tests, Vol. C2.14.
SPECIAL TOXICITY

1. Guinea Pig: Skin sensitization study, Vol. C2.13.

Studies Not Reviewed in this IND: The 4-wk inhalation toxicity study in rat with Metered-dose HFA-formulation was not reviewed because a complete study report was not available. -Since the proposed route of administration is inhalation, toxicity and special toxicity studies conducted with routes other than inhalation were not reviewed. The following is a list of studies not reviewed:

TOXICOLOGY

b(4)

SPECIAL TOXICITY

Studies Previously Reviewed: None.

Note: Portions of this review were excerpted directly from the sponsor's submission.

b) Inhibition of Anti-CD3-induced Cytokine Synthesis in Mouse TH2 Lymphocytes:

Both R-Ciclesonide and its metabolite inhibited the synthesis of interleukins 4 and 5 with metabolite being twice as potent as the parent drug; S-Ciclesonide was not studied:

Test Compound	IC ₅₀ (nM)	
	Inhibition of synthesis of IL-4	Inhibition of synthesis of IL-5
R-Ciclesonide	0.42	0.27
Metabolite of R-Ciclesonide	0.19	0.12
Budesonide	0.32	0.22

c) Inhibition of Interleukin-2 Production of CD3-Stimulated Human Peripheral Blood Mononuclear Cells (PMBCs):

The metabolite of R-Ciclesonide was more potent than R-Ciclesonide; S-Ciclesonide was least potent:

Test Compound	IC ₅₀ (nM)
R-Ciclesonide	4.5
S-Ciclesonide	56.3
Metabolite of R-Ciclesonide	0.65
Budesonide	1.3

d) Inhibition of Con A-Induced Proliferation of PMBCs:

Metabolite of R-Ciclesonide was more potent than R-Ciclesonide; S-Ciclesonide was not studied.

Test Compound	IC ₅₀ (nM)
R-Ciclesonide	14.6
Metabolite of R-Ciclesonide	1.4
Budesonide	1.4

**APPEARS THIS WAY
ON ORIGINAL**

PHARMACOLOGY: *IN VIVO* STUDIES FOR ANTI-INFLAMMATORY ACTIVITY

Rat: Inhibition of formation of granulation tissue (proliferative activity) in subcutaneously implanted Cotton Pellets:

R-Ciclesonide was more potent than S-Ciclesonide or Budesonide.

b(4)

Test Compound	ED ₅₀ (µg/pellet)
R-Ciclesonide	2.0
S-Ciclesonide	23.7
Budesonide	33.5

Systemic effect seen at 100-500 µg/pellet. ED₅₀ for thymic involution were 302 and 153 µg for R-Ciclesonide and Budesonide, respectively.

In this study, for the effect on the pellet and on the thymus weight, the systemic/local activity ratio was 4.6 for Budesonide and ≥ 150 for the R-epimer of Ciclesonide.

Mice: Inhibition of Croton Oil-induced ear inflammation:

% inhibition due to R-Ciclesonide (range: 18-68%) and its metabolite (range: 14-59%) at dose range of 1-100 µg/ear was comparable; S-Ciclesonide was not studied.

Rat: Inhibition of Bradykinin-induced mucosal leakage in trachea in situ:

At doses of 1-100 µM for R-Ciclesonide and 3-300 µM for Budesonide, there was 23-40% and 9-35% inhibition of leakage in trachea. R-Ciclesonide was more potent than Budesonide.

Test Compound	ID ₂₅ (25% Inhibition Dose) µM
R- Ciclesonide	14.7
Budesonide	39.5

Rat: Effects of single intratracheal powder instillation of Ciclesonide on cell accumulation and protein concentration in bronchoalveolar lavage (BAL) of Ovalbumin-sensitized animals.

At 1.0 and 10.0 mg/kg (i.t.), R-Ciclesonide significantly ($p \leq 0.01$) inhibited total cell (53-89%), Neutrophil (43-86%), Lymphocytes (52-64%), and Eosinophil (66-96%) accumulation, as well as influx of protein (43-91%) in BAL.

SUMMARY OF PHARMACOLOGY

Ciclesonide is a prodrug as shown by 100-fold relative binding affinity of its metabolite to glucocorticoid receptor (rat lung cytosol) than drug itself. The drug or its metabolite had no affinity for the estrogen receptor and very low affinity for progesterone and testosterone receptors. The drug exhibited immunosuppressive properties in various *in vitro* models (Inhibition of Concanavalin A-Stimulated Rat Spleen Cells; Inhibition of Anti-CD3-induced Cytokine Synthesis in Mouse TH2 Lymphocytes; Inhibition of Interleukin-2 Production of CD3-Stimulated Human Peripheral Blood Mononuclear Cells (PMBCs); Inhibition of Con A-Induced Proliferation of PMBCs). Its anti-inflammatory activity was shown in mice (Inhibition of Croton Oil-induced ear inflammation) and rats (Inhibition of formation of granulation tissue/ proliferative activity in subcutaneously implanted Cotton Pellets). The drug was shown to have pharmacodynamic activity relevant to proposed indication in rat models (Inhibition of Bradykinin-induced mucosal leakage in trachea; Effects of single intratracheal powder instillation of Ciclesonide on cell accumulation and protein concentration in bronchoalveolar lavage (BAL) of Ovalbumin-sensitized animals). R-Ciclesonide or its metabolite were more potent than the structurally similar glucocorticoid steroid Budesonide. R-Ciclesonide > S-Ciclesonide, thus R-Ciclesonide was developed. Systemic/local ratio for R-Ciclesonide was higher compared to Budesonide.

b(4)

SAFETY PHARMACOLOGY

CNS Effects:

Rats and Mice: At 20 mg/kg (i.v.), no effect on behavior of female rats or mice (behavioral parameters studied by Irwin, 1966).

Effects on Cardiovascular and Respiratory System:

Cats: A 15 min. i.v. infusion of 0.1, 0.3, and 1.0 mg/kg did not induce noticeable cardiovascular (arterial pressure, heart rate, left ventricular pressure and contractility, central venous pressure, ECG) and respiratory effects (respiratory rate, tidal volume, and respiratory minute volume) in anaesthetized cats.

SUMMARY OF SAFETY PHARMACOLOGY

Ciclesonide had no significant effects on CNS (behavioral parameters) in mice and rats and cardiovascular and respiratory system in cats.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

ABSORPTION: When the drug (C^{14} -R-Ciclesonide) was administered via i.v., exposure (AUC_{0-4h}) in rat was comparable to exposure (AUC_{0-24h}) in dog. The $T_{1/2}$ was shorter in rat (6.8 hours) compared to dog (17 hours). When the drug was given orally, the T_{max} in rats and dogs were comparable. The $T_{1/2}$ in dogs (14 hours) was twice of that in rats (7.6 hours). The C_{max} values for dogs were greater than those for rats. The oral bioavailability of the drug in dogs (66%) was about two-fold of that in rats (28%). In dog, inhalation administration of the drug resulted in high C_{max} indicating high bioavailability. The pharmacokinetic parameters for rats and dogs are shown in the Table below:

PHARMACOKINETIC PARAMETERS

Parameter	Rat	Dog
ORAL		
Dose (mg/kg)	1.0	1.0
C_{max} (ng/mL)	41	152
T_{max} (hours)	0.25-10	0.25-1.5
F (%)	28%	66%
AUC (mg.hr/L)	0.42 (0-4 h)	0.937 (0-14 h)
$t_{1/2}$ (hours)	7.6	14.0
INTRAVENOUS		
Dose (mg/kg)	1.0	0.1
C_{max} (ng/mL)	----	82.1
T_{max} (hours)	----	0.03
AUC (mg.hr/L)	1.48 (0-4 h)	0.142 (0-24 h)
$t_{1/2}$ (hours):	6.8	17.0
INHALATION		
Dose (mg/kg)		0.006
C_{max} (ng/mL)		0.34
T_{max} (hours)		0.5
AUC (mg.hr/L)		0.0005 (0-4 h)

---- Data not provided.

DISTRIBUTION: In rat, following administration of [¹⁴C]-R-Ciclesonide (1 mg/kg) via i.v., p.o. or i.t. routes, distribution of radioactivity was as follows (all units in µg/g):

I.V. Route: Lung (14.2)>Heart (7.9)>thyroid (4.2)>kidney, liver (2.8)>G.I. tract (1.9)>Adrenals (1.8)>thymus (0.5).

P.O. Route: G.I. Tract (17.7)>liver (0.2)>kidney (0.12)>thyroid, adrenal, spleen, skin (0.04)>lung (0.03)>thymus (0.01).

I.T. Route: Trachea (73.1)>Thyroid (7.2)>G.I. tract (2.6)>lung (0.8)>Eye (0.6)>thymus (0.02).

METABOLISM: The drug (³H-R-Ciclesonide) was more rapidly metabolized to major metabolite (M₁) *ex vivo* in lung homogenates from rat (t_{1/2} ~ 2 hours) than those from dog (t_{1/2} ~ 11 hours). In liver homogenates from rats, there was marked sex difference in the metabolism of the drug (t_{1/2}: ♂: 51 min., ♀: 6 min.). In rat liver microsomes (S9 fraction), the drug was rapidly metabolized (t_{1/2}=18 minutes). In dog liver homogenates (both sexes), the drug was quite rapidly (t_{1/2}=17 min.) metabolized to M₁ metabolite. In homogenates from mouse skin, t_{1/2} of metabolism to M₁ metabolite was about 4 hours. Minor metabolites were M₂, M₃, M₄, and M₅. Metabolic pathway for Ciclesonide is shown in Figure 1 (See page 13).

EXCRETION: In rats, most radiolabelled drug was excreted via feces (81-82% of dose; p.o. or i.v.) than via urine (8-9% of dose; p.o. or i.v.). Total Recovered drug was 89-91% of dose (p.o. or i.v.). In dogs, most drug excreted via feces (81-86% of dose; p.o. or i.v.) than via urine (6-8% of dose; p.o. or i.v.). Total recovered drug in dogs constituted 87-94% of dose (p.o. or i.v.).

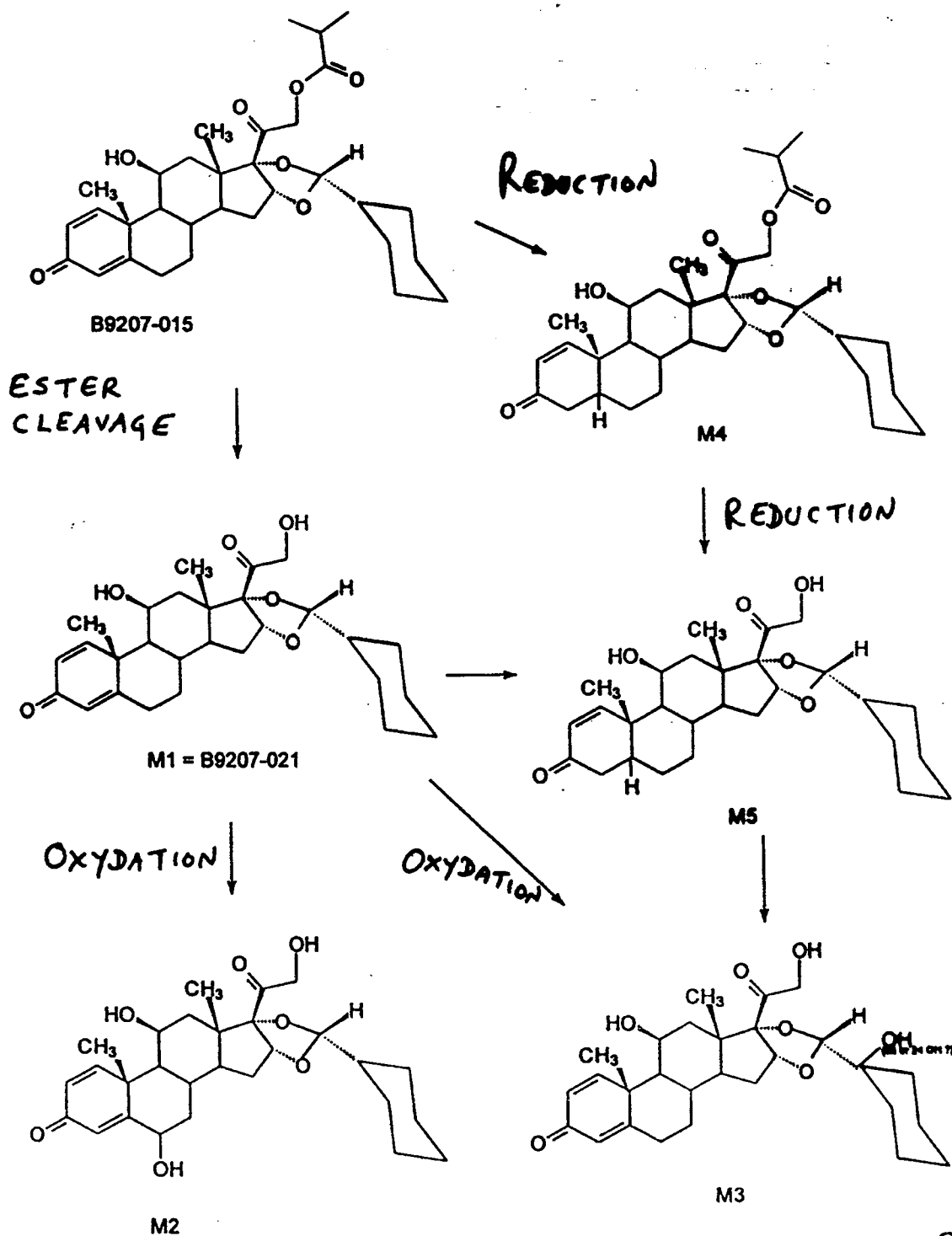


Figure 1: Metabolism of Ciclesonide in rats.
TOXICOLOGY

ACUTE, SINGLE DOSE, TOXICITY:

Mice: Acute Toxicity (i.p.)

Byk Gulden Study 164/94, 30 November, 1994, Vol. C2.5

15 animals/Sex (5/Sex/group) were administered 50, 100, and 200 mg/kg of the drug (Batch MS181) solution prepared in sesame oil via i.p. route (dosing volume 20 mL/kg); animals of control group (2/Sex) received sesame oil alone. Treatment resulted in 2 mortalities (1/Sex) at the end of the observation period (14 days) at 200 mg/kg (HD). HD resulted in atrophy of thymus (σ : 4/5; ♀ : 3/5), spleens (σ : 5/5; ♀ : 5/5), and adrenals (σ : 5/5; ♀ : 5/5). Minimum Lethal Dose was 200 mg/kg.

Mice: Acute Toxicity (p.o.)

Byk Gulden Study 94/94, 01 August, 1994, Vol. C2.5

5 animals/Sex were administered 2000 mg/kg of the drug (Batch MS181) suspension (prepared with Tween 80, Keltrol RD, and distilled water) orally with a gastric cannula (dosing volume 20 mL/kg); control animals (2/Sex) received same vehicle as the animals of the treatment group. No signs of toxicity were observed. Thus, Minimum Lethal Dose was greater than 2000 mg/kg.

Rat: Acute Toxicity (i.p.)

Byk Gulden Study 165/94, 30 November, 1994, Vol. C2.5

15 animals/Sex (5/Sex/group) were administered 50, 100, and 200 mg/kg of the drug (Batch MS181) solution prepared in sesame oil via i.p. route (dosing volume 20 mL/kg); animals of control group (2/Sex) received sesame oil alone. Treatment resulted in 2 mortalities (1/Sex) on days 5 (female) and 6 (male) at 200 mg/kg (HD). HD resulted in high graded atrophy of thymus and spleens (σ : 5/5; ♀ : 5/5). Minimum Lethal Dose was 200 mg/kg.

Rat: Acute Toxicity (p.o.)

Byk Gulden Study 106/94, 01 August, 1994, Vol. C2.5

5 animals/Sex were administered 2000 mg/kg of the drug (Batch MS181) suspension (prepared with Tween 80, Keltrol RD, and distilled water) orally with a gastric cannula (dosing volume 20 mL/kg); control animals (2/Sex) received same vehicle as the animals of the treatment group. There was no mortality reported. Treatment resulted in follicular atrophy in the spleen (σ : 3/5; f : 4/5) and cortical atrophy of the adrenals (σ : 3/5; f : 3/5). Minimum Lethal Dose was greater than 2000 mg/kg.

SUBCHRONIC AND CHRONIC, MULTIPLE DOSE, TOXICITY:

Rat: 4-wk Inhalation Toxicity with Dry Powder Formulation Byk Gulden Study 121E/94, 28 June, 1994, Vol. C2.8

Study Dates: January 31, 1994 to March 29, 1994

Testing Lab: _____

b(4)

Test Article: The drug substance (Batch GU03/207) was aerosolized using a microfeeding system and a pressurized air dispersion nozzle. Particles $\sim$ μm were removed by a virtual impactor.

GLP: The study was accompanied by a signed GLP statement.

METHODS

Species/Strain: Sprague-Dawley rats.

Animals: 60/Sex; 10/Sex/group.

Route: Dry powder inhalation.

Dosage: 0 (Air Control); 15.3 $\mu\text{g}/\text{kg}/\text{day}$ (LD); 50.5 $\mu\text{g}/\text{kg}/\text{day}$ (MD); 156.5 $\mu\text{g}/\text{kg}/\text{day}$ (HD); 156.5 $\mu\text{g}/\text{kg}/\text{day}$ (Recovery group). The dose was calculated with a respiratory minute volume $V_{\text{min}} = 2.1 \times (\text{body weight})^{0.75}$ (Guyton, 1947), 1h respiratory volume (VR) = $60 \times V_{\text{min}}$, aerosol concentrations (1, 3, and 10 mg/m^3) and mean body weights from this study, 50% deposition, and 100% resorption of the inhaled particles. Particle size (MMAD) was $\sim$ μm .

Duration of Exposure: 4 weeks; 1 hr. daily.

Clinical Observations: Daily: before, during, and after exposure; detailed observations: weekly.

Body Weights: Weekly commencing 1 week pretrial.

Food Consumption: Weekly commencing 1 week pretrial.

Ophthalmoscopy: Once pretrial and once at the end of the exposure period (Control and

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HD only).

Hematology: Once pretrial and once prior to the end of the exposure period.

Clinical Chemistry: Once pretrial and once prior to the end of the exposure period.

Urinalysis: End of exposure period.

Drug Levels: Blood samples were collected but not analyzed.

Organ Weights, Gross- and Histopathology: At termination.

**APPEARS THIS WAY
ON ORIGINAL**

RESULTS

Mortality: There were no mortalities.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Decrease in body weight gain (10%) at HD was reversible as shown by HD Recovery group.

Food Consumption: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Hematology: In HD females, decrease in lymphocyte counts (40%) was reversible.

Clinical Chemistry: Increase in bilirubin (79%) in HD females was reversible.

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: Treatment resulted in dose dependent decrease in the relative weights of thymus (σ : MD 18%, HD 44%; ♀ : MD 16%, HD 44%); the recovery HD group animals regained thymus weights.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Treatment resulted in diffuse lymphoid depletion of the thymic cortex (σ : MD 6/10, HD 9/10; ♀ : Control 1/10, LD 1/10, MD 3/10, HD 10/10) which was not seen in recovery HD group.

NOAEL: 50.5 $\mu\text{g}/\text{kg}/\text{day}$.

Rat: 4-wk Dose Ranging Inhalation Toxicity with Metered-dose HFA-formulation
Byk Gulden Study 167E/96, 17 October, 1996, Vol. C2.8

5 animals/Sex were administered 184 µg/kg/day of the drug (Batch MS427/C) solution in 8% ethanol and 92% HFA-134a (dosing volume 20 mL/kg); 5 animals/Sex represented control group that was exposed to air only. Treatment resulted in decreased body weights 16-18%), decreased WBC counts (26-29%) and lymphocytes (32-22%), decreased relative thymus weights (46%) but no toxicologically significant treatment-related changes in histopathology. The NOAEL was <184 µg/kg/day.

Rat: 26-wk Inhalation Toxicity with Dry Powder Formulation
Byk Gulden Study 138E/95, 26 June, 1995, Vol. C2.10

Study Dates: June 07, 1994 to January 11, 1995

Testing Lab: _____

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Test Article: Ciclesonide Dry Powder

GLP: The study was accompanied by a signed GLP statement.

METHODS

Species/Strain: Rat (Sprague-Dawley).

Animals: 100/Sex; 20/Sex/group (treatment groups and air control); 10/Sex/group (Recovery HD and control groups).

Route: Inhalation (nose-only).

Dosage: Air Control; 16.5 µg/kg/day (LD); 47.5 µg/kg/day; 166.0 µg/kg/day (HD). The dose was calculated with a respiratory minute volume $V_{\min} = 2.1 \times (\text{body weight})^{0.75}$ (Guyton, 1947), 1h respiratory volume (VR)=60 X $V_{\min}$, aerosol concentrations (1, 3, and 10 mg/m³) and mean body weights from this study, 50% deposition, and 100% resorption of the inhaled particles. Particle size (MMAD) was $\text{---}\mu\text{m}$.

Duration of Exposure: 26 weeks; 1 hour/day.

Clinical Observations: Daily.

Body Weights: Weekly.

Food Consumption: Weekly.

Ophthalmoscopy: One week prior to exposure and during the last week of exposure.

Hematology: One week pre-exposure and during last week of exposure.

Clinical Chemistry: One week pre-exposure and during last week of exposure.

Urinalysis: Prior to final sacrifice.

Drug Levels: Blood samples were collected but not analyzed.
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortality: There was one drug-related mortality (HD) which was associated with dyspnea caused by severe mycosis of trachea.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in decreased body weights (σ : HD 15%, Recovery HD: 11%; φ : MD 10%, HD 21%, Recovery HD 12%).

Food Consumption: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Hematology: Treatment resulted in decrease in WBC counts (σ : HD 28%; φ : LD 17%, MD 19%, HD 28%), Lymphocyte counts (σ : HD 33%; φ : LD 16%; MD 20%; HD 37%), Lymphocyte % (φ : HD 12%) and increase in segmented Neutrophil % (σ : 32%; φ : HD 60%). For WBC and lymphocyte counts, females were more sensitive to the effect of the drug than males.

Clinical Chemistry: Treatment resulted in decreased choline esterase (σ : HD 15%; φ : HD 13%) and an increase in total bilirubin (σ : HD 64%; φ : 50%), blood glucose (σ : HD 18%), and glutamic pyruvic transaminase (φ : HD 68%).

Urinalysis: Treatment resulted in decreased sodium (φ : HD 13%) and inorganic phosphate (σ : MD 35%, HD 46%; φ : MD 16%, HD 27%), increased potassium (φ : LD 31%, MD 13%, HD 29%), and higher incidences of ketone bodies (σ : Control 9/18, LD 12/20, MD 16/19, HD 19/20; φ : HD 2/20) and presence of leukocytes (σ : Control 11/18, LD 17/20, MD 18/19, HD 19/20; φ : Control 2/20, LD 2/19, MD 3/20, HD 8/20).

Organ Weights: There was dose dependent decrease in the absolute weights of thymus (σ : MD 17%, HD 50%, Recovery: 8%; φ : LD 18%, MD 27%, HD 45%, Recovery: 18%), slight decrease in liver weights (φ : HD 10%, Recovery: 6%), and slight increase in the weights of brain (σ : HD 5%, Recovery: 5%).

Relative weights of thymus (σ : MD 18%, HD 41%, Recovery: 20%; φ : LD 16%, MD

18%, HD 35%, Recovery: no difference), liver (σ : MD 9%, HD 19%, Recovery: 11%; ♀ : HD 14%, Recovery: no difference), and brain (σ : MD 10%, HD 21%, Recovery: 16%; ♀ : MD 13%, HD 27%, Recovery: 12%)

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Toxicologically significant treatment-related effects are as follows:

Organ	Histopathologic Findings	
	Finding	Incidence
Thymus	Lymphoid depletion of cortex, Severe: Data show complete recovery.	σ : HD 1/20, Recovery: 0/10 ♀ : HD 3/20, Recovery: 0/10
Lymph Node	Mesenteric LN depletion: Data show complete recovery.	σ : HD: 12/20, Recovery: 0/10; ♀ : HD: 8/20, Recovery: 0/10.
Lung	Multifocal alveolar histiocytosis, slight: Data show complete recovery in females.	σ : C 3/20, LD 6/20, MD 8/20, HD 10/20, Recovery HD: 1/10; ♀ : LD 6/20, MD 2/20, HD 3/20, Recovery: C 1/10, HD 1/10).
	Multifocal interstitial mononuclear. cell infiltration: slight/moderate:	σ : C 4/20, LD 5/20, MD 12/20, HD 6/20, Recovery: C 1/10, HD 6/10 ♀ : Not significant.
	BALT (Bronchus-associated lymphoid tissue), atrophy: Data showed complete recovery in males.	σ : MD: 7/20; HD: 18/20, Recovery: 0/10; ♀ : C 1/20; HD 16/20, Recovery: 1/10
Mammary Gland	Glandular Development, moderate+severe: Data showed complete recovery in males. (typical steroid effect in humans)	σ : LD 1/20, MD 3/20, HD 6/20, Recovery: 0/10; ♀ : MD 9/20, HD 14/20,

Recovery: 3/10

NOAEL: There was no clear NOAEL.

Dog: 4-wk Inhalation Toxicity with Dry Powder Formulation

Byk Gulden Study 205/94, 9 March, 1995, Vol. C2.9

Study Dates: 27 June, 1994 to 22 August, 1994

Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany

Test Article: Ciclesonide Dry Powder

GLP: The study was accompanied by a signed GLP statement.

METHODS

Species/Strain: Dogs (Beagle).

Animals: 18/Sex; 4/Sex/group (Control, LD, MD); 6/Sex/group (HD).

Route: Inhalation (Head only).

Dosage: Air Control; 15 µg/kg/day (LD); 50 µg/kg/day (MD); 100 µg/kg/day (HD). The dose (µg/kg/day) was calculated using following assumptions and formula:

Respiratory minute volume in dog = 5 L/minute

Body mass = 10 kg

Exposure duration = 30 minutes

Deposition of test substance in respiratory tract = 50%

Aerosol Concentration = 2.2, 7.5, 14.5, and 15.2 µg/L for LD, MD, HD, and HD

Recovery groups, respectively.

Particle size (MMAD) = — µm.

$$\frac{5 \text{ (L/min)} \times 30 \text{ (min)} \times \text{mean aerosol concentration (}\mu\text{g/L)} \times 0.5}{10 \text{ (kg)}}$$

Duration of Exposure: 4 weeks (30 minutes/day).

Clinical Observations: Daily.

Body Weights: Daily during first 2 weeks prior to dosing; Two-times/week during exposure period.

Food Consumption: Daily.

Ophthalmoscopy: Weeks -2, 4, and 8 (recovery animals).

Hematology: Weeks -2, -1, 1, 4, and 8 (recovery animals).

Clinical Chemistry: Weeks -2, -1, 1, 4, and 8 (recovery animals).

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Urinalysis: Weeks -1, 4, and 8 (recovery animals).
Drug Levels: Blood samples were collected but not analyzed.
Organ Weights, Gross- and Histopathology: At termination.

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RESULTS

Mortality: There was no mortality.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: No toxicologically significant treatment-related effects.

Food Consumption: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Serum Cortisol Concentration: Suppression of cortisol was seen in 2 LD males, 2 MD males and 2 MD females; significant suppression was seen in all HD animals.

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: Treatment resulted in decreased relative weights of adrenals (σ : MD 18%, HD 28%; ♀ : MD 14%, HD 34%).

Gross Pathology: Incidence of emphysema of the lung was reversible in HD recovery animals:

σ : Control 2/4, LD 1/4, MD 2/4, HD 4/4, Recovery 1/2;
 ♀ : Control 2/4, LD 1/4, MD 4/4, HD 4/4, Recovery 0/2

Histopathology: Toxicologically significant treatment-related effects are as follows:

Organ	Histopathologic Findings	
	Finding	Incidence
Thymus	Cysts	♂: LD 2/4, MD 2/4, HD 3/4, Recovery HD 0/2 ♀: MD 1/4, HD 4/4 Recovery HD 0/2
Adrenal	Zona fasciculata regeneration	♂: HD 1/4, Recovery HD 0/2 ♀: HD 2/4, Recovery HD 0/2
Lung	Alveolar emphysema	♂: Control 2/4, LD 1/4, MD 2/4, HD 4/4 Recovery HD 1/2 ♀: Control 2/4, LD 1/4, MD 4/4, HD 4/4 Recovery HD 0/2

NOAEL: ♂: 50 µg/kg/day
♀: 15 µg/kg/day

Dog: 52-wk Inhalation Toxicity with Dry Powder Formulation
Byk Gulden Study 116/96, 11 March, 1997, Vol. C2.12

Study Dates: 18 May, 1995 to 11 March, 1997
Testing Lab: Byk Gulden Institute of Pathology and Toxicology
Test Article: Ciclesonide Dry Powder
GLP: The study was accompanied by a signed GLP statement.

METHODS

Species/Strain: Dogs (Beagle).
Animals: 18/Sex; 4/Sex/group (Air Control, LD, MD); 6/Sex/group (HD): of these, 2/Sex/group were used for Recovery group.
Route: Inhalation (Head only).
Dosage: Air Control; 18 µg/kg/day (LD); 47 µg/kg/day (MD); 92 µg/kg/day (HD). The dose (µg/kg/day) was calculated using following assumptions and formula:
Respiratory minute volume in dog = 5 L/minute
Body mass = 10 kg
Exposure duration = 30 minutes
Deposition of test substance in respiratory tract = 50%
Aerosol Concentration = 2.4, 6.3, 12.2, and 12.2 µg/L for LD, MD, HD, and HD Recovery groups, respectively.
Particle size (MMAD) = 4 µm (90% particles).

$$\frac{5 \text{ (L/min)} \times 30 \text{ (min)} \times \text{mean aerosol concentration (}\mu\text{g/L)} \times 0.5}{10 \text{ (kg)}}$$

Duration of Exposure: 52 weeks (30 minutes/day).
Clinical Observations: Daily.
Body Weights: Weekly during -3, -2, and -1 weeks, twice-weekly thereafter.
Food Consumption: Daily.
Ophthalmoscopy: Weeks -1, 25, 51, and 56 (recovery group animals).
Electrocardiography: Weeks -2, -1, 13, 25, 50, and 56 (recovery group animals).
Hematology: Weeks -2, -1, 13, 25, 50, and 56 (recovery group animals).
Clinical Chemistry: Weeks -2, -1, 13, 25, 50, and 56 (recovery group animals).
Urinalysis: Weeks -1, 26, 52, and 56 (recovery group animals).
Drug Levels: Blood samples were collected but not analyzed.
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortality: There were no mortalities.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: No toxicologically significant treatment-related effects.

Food Consumption: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Electrocardiography: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: Treatment resulted in decreased weights of adrenals (σ : LD 14%, MD 42%, HD 40%; ♀ : LD 35%, MD 41%, HD 62%).

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Toxicologically significant treatment-related effects are as follows:

Organ	Histopathologic Findings	
	Finding	Incidence
Thymus	Cysts	♀: LD 2/4, MD 1/4, HD 3/4, HD Recovery HD: 0/2
Adrenal	Cortical atrophy	♂: LD 2/4, MD 4/4, HD 4/4 Recovery 1/2 ♀: LD 0/4, MD 2/4, HD 2/4 Recovery 1/2
Lymph Nodes	Follicular atrophy (B cell)	♂: HD: 3/4 ♀: HD: 2/4
Nasal Cavity	Incidence of Intraepithelial cysts in the rostral section of 3 nasal sections	Nasal Cavity 1: ♂: Control 1/4, LD 2/4, MD 1/4, HD 3/4 Recovery 1/2 ♀: Control 1/4, LD 3/4, MD 3/4, HD 3/4 Recovery 2/2
	Maxilloturbinates:	
	Osseous (bone) disorganization	♂: C 1/4; LD 3/4; MD, HD 4/4 Recovery 0/2 ♀: C 0/4; LD 4/4; MD 3/3, HD 4/4 Recovery 0/2
	Chondrosis (cartilagenous bone formation)	♂: C 1/4, LD 2/4, MD 1/4, HD 3/4 Recovery 2/2 ♀: C 0/4, LD 1/4, MD 3/4, HD 2/4 Recovery 2/2
	Osteofibrosis of turbinalia	♂: LD 2/4, MD 2/4, HD 4/4; Recovery 2/2 ♀: LD 2/4, MD 3/4, HD 3/4; Recovery 2/2
Lung	Thickened alveolar septa/interstitial thickening	♂: LD 1/4, MD 2/4, HD 4/4 Recovery 0/2.
Skin	Hair follicle regression: ↓ Thickness of dermis:	♂: HD 2/4 ♂: MD 1/4, HD 2/4 ♀: HD 1/4.
Testes	Spermiogenic disturbance	♂: LD 2/4, MD 3/4, HD 1/4 Recovery 1/2
Ovary	Atrophy	♀: HD 4/4

NOAEL: There is no clear *NOAEL*.

**APPEARS THIS WAY
ON ORIGINAL**

Dog: 4-wk Inhalation Toxicity with Metered-dose CFC-formulation
Byk Gulden Study 114E/94, 27 June, 1994, Vol. C2.13

Study Dates: March, 1988 to July, 1988

Testing Lab: _____

Test Article: The drug was supplied in aerosol cans with a metered-dose valve delivering 25 and 50 µg/puff. Each 10 mL Vehicle consisted of Ciclesonide container consisted of 15 mg Sorbitan trioleate (Span 85), 5.55 g Trichloromonofluoromethane, and 8.35 g Dichlorodifluoromethane.

GLP: GLP statement was not included.

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METHODS

Species/Strain: Dogs (Beagle).

Animals: 8/Sex; 2/Sex/group.

Route: Inhalation (via mouth piece adapted to the muzzle of the animal).

Dosage: Vehicle Control; 20 µg/kg/day (LD); 60 µg/kg/day (MD); and 180 µg/kg/day (HD). These doses were delivered via metered-dose valve; each actuation consisted of 200 µg. The animals were given the drug or the vehicle using an aerosol with an expansion chamber to permit nebulization. One, three, and nine puffs were delivered to the animals of LD, MD, and HD groups, respectively. Dose calculation was based on assumptions that the body weight was 10 kg/animal and that resorption of the inhaled particles was 100%. However, in the absence of information on deposition factor and vapor concentration, dose levels were probably overestimated.

Duration of Exposure: 4 weeks.

Clinical Observations: Daily.

Body Weights: Pre-dosing and at the end of the treatment period.

Hematology: Prior to the start of the treatment and at the end of the study.

Clinical Chemistry: Prior to the start of the treatment and at the end of the study.

Urinalysis: Prior to the start of the treatment and at the end of the study.

Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortality: There were no mortalities during the study.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: Treatment resulted in decreased plasma Cortisol levels (♂: MD 30%, HD 28%; ♀: LD 22%, HD 10%). No other toxicologically significant treatment-related effects.

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: Treatment resulted in an increase in relative weight of spleens: (♂: LD 68%, MD 79%, HD 68%; ♀: LD 42%, MD 88%, HD 100%).

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Alveolar microhemorrhage was reported in 2/4 animals (#5 and #13) of MD group but not in LD or HD animals; According to the sponsor, this finding might be drug-related.

NOAEL: 180 µg/kg/day.

Dog: 26-wk Inhalation Toxicity with Metered-dose CFC-formulation
Byk Gulden Study 115E/94, 27 June, 1994, Vol. C2.13

Study Dates: December 1988 to September, 1989

Testing Lab: _____

Test Article: The drug was supplied in aerosol cans with a metered-dose valve delivering 25 and 50 µg/puff. Each 10 mL Vehicle consisted of Ciclesonide container consisted of 15 mg Sorbitan trioleate (Span 85), 5.55 g Trichloromonofluoromethane, and 8.35 g Dichlorodifluoromethane.

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GLP: GLP statement was not included.

METHODS

Species/Strain: Dogs (Beagle).

Animals: 8/Sex; 2/Sex/group.

Route: Inhalation (via mouth piece adapted to the muzzle of the animal).

Dosage: Vehicle Control; 2.5 µg/kg/day (LD); 10 µg/kg/day (MD); and 40 µg/kg/day (HD). These doses were delivered via metered-dose valve; each actuation consisted of 200 µg. The animals were given the drug or the vehicle using an aerosol with an expansion chamber to permit nebulization. One, three, and nine puffs were delivered to the animals of LD, MD, and HD groups, respectively. Dose calculation was based on assumptions that the body weight was 10 kg/animal and that resorption of the inhaled particles was 100%. However, in the absence of information on deposition factor and vapor concentration, dose levels were probably overestimated.

Duration of Exposure: 26 weeks.

Clinical Observations: Daily.

Body Weights: Pre-dosing, monthly, and at the end of the treatment period.

Hematology: Prior to the start of the treatment, 3 months post-treatment, and at the end of the study.

Clinical Chemistry: Prior to the start of the treatment, 3 months post-treatment, and at the end of the study.

Urinalysis: Prior to the start of the treatment, 3 months post-treatment, and at the end of the study.

Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortality: There were no mortalities during the study.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: Treatment resulted in decreased plasma Cortisol levels (σ : LD 34%, MD 29%, HD 29%; φ : LD 30%, MD 28%, HD 39%). No other toxicologically significant treatment-related effects.

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: An increase in thymus weights at LD and MD and a decrease at HD (σ : LD 65% $\uparrow$, MD 89% $\uparrow$, HD 33% $\downarrow$; φ : LD 19% $\uparrow$, MD 75% $\uparrow$, HD 28% $\downarrow$) was not explained.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: No toxicologically significant treatment-related effects.

NOAEL: 40 μ g/kg/day.

SUMMARY OF TOXICOLOGY

In a single dose lethality (i.p.) study in mice (50, 100, and 200 mg/kg), HD resulted in 2 mortalities and atrophy of thymus, spleens, and adrenals. Minimum lethal dose was 200 mg/kg. A single dose lethality oral study in mice (2000 mg/kg) resulted in no signs of toxicity and Minimum lethal dose was greater than 2000 mg/kg. In a single dose lethality (i.p.) study in rats (50, 100, and 200 mg/kg), HD resulted in 2 mortalities and atrophy of thymus and spleens. Minimum lethal dose was 200 mg/kg. A single dose lethality oral study in rats (2000 mg/kg) resulted in no mortality. Toxicologically significant treatment-related effects were follicular atrophy of spleen and cortical atrophy of the adrenals. Minimum lethal dose was greater than 2000 mg/kg.

In a 4-week inhalation toxicity rat study with DPI formulation, treatment (15.3, 50.5, and 156.5 $\mu\text{g}/\text{kg}/\text{day}$) resulted in a decrease in lymphocyte counts and an increase in bilirubin in HD females. There was a decrease in the relative weights of thymus accompanied with diffuse lymphoid depletion of thymic cortex. The NOAEL was 50.5 $\mu\text{g}/\text{kg}/\text{day}$ and thymus was the target organ of toxicity. In a 4-week dose ranging study in rats with MDI (HFA) formulation, treatment (184 $\mu\text{g}/\text{kg}/\text{day}$) resulted in decreased body weights, WBC counts, lymphocytes, and relative thymus weights. The NOAEL was <184 $\mu\text{g}/\text{kg}/\text{day}$ and again, thymus was the target organ of toxicity.

When the drug (16.5, 47.5, and 166.0 $\mu\text{g}/\text{kg}/\text{day}$) was given to rats via inhalation (DPI formulation) for 26 weeks, treatment resulted in one drug-related mortality (HD) and decreased body weights at HD in males and MD in females. Treatment resulted in a decrease in WBC and Lymphocyte counts at LD, Lymphocyte % at HD and increase in segmented Neutrophil % at HD. Clinical Chemistry changes were decreased choline esterase at HD, and an increase in total bilirubin, blood glucose, and glutamic pyruvic transaminase at HD. Treatment resulted in decreased sodium at HD and inorganic phosphate at MD, and increased potassium and higher incidences of ketone bodies and leukocytes at LD. There was dose dependent decrease in the absolute and relative weights of thymus at LD, decrease in liver weights at HD, and increase in the weights of brain at HD. Histopathological changes were: lymphoid depletion of cortex of thymus and mesenteric lymph node depletion at HD; multifocal alveolar histiocytosis in lungs at LD, multifocal interstitial mononuclear cell infiltration in lungs at LD (not significant in females); atrophy in BALT (Bronchus-associated lymphoid tissue at MD; and glandular development in mammary glands at LD. Most of these effects were either typical glucocorticoid steroid effects or local toxic effects due to the formulation (particles of dry powder). Multifocal interstitial mononuclear cell infiltration in lungs is probably caused by the physical nature of the test article (dry powder). Although multifocal alveolar

histiocytosis in lungs was most likely caused by the physical nature of the drug formulation (dry powder particles), it has been known from the published studies on other compounds that histiocytosis may not be fully reversed in as long as 6 months recovery time. Therefore, the sponsor should be asked to explain the significance of histiocytosis for this drug. Moreover, no acceptable studies with MDI formulation (containing HFA and ethanol) are available at the present time to ascertain whether or not histiocytosis is seen with the MDI (HFA) formulation. Until such time that additional information is available to explain the significance of histiocytosis in assessing safety of MDI (HFA) formulation, it is reasonable to assume that there is no clear NOAEL for this study. The target organs of toxicity were thymus, mesenteric lymph node, lung, and mammary gland.

In a 4-week inhalation toxicity study in dogs with DPI formulation, treatment (15, 50, and 100 $\mu\text{g}/\text{kg}/\text{day}$) resulted in suppression of cortisol at LD and decreased weights of adrenals at MD. Histopathological changes were: alveolar emphysema of the lungs at LD; incidences of zona fasciculata regeneration in adrenals at HD; and incidence of cysts in thymus at LD. The NOAEL was 50 $\mu\text{g}/\text{kg}/\text{day}$ for males and 15 $\mu\text{g}/\text{kg}/\text{day}$ for females. The target organs of toxicity were adrenal, lung, and thymus.

In a 52-week inhalation toxicity study in dogs with DPI formulation, treatment (18, 47, and 92 $\mu\text{g}/\text{kg}/\text{day}$) resulted in decreased weights of adrenals at LD. Histopathological changes were: Cortical atrophy of adrenals at LD and increased incidence of intraepithelial cysts in the rostral section of 3 nasal sections of nasal cavity (all at LD). In the maxilloturbinates of nasal cavity, LD resulted in chondrosis, osteofibrosis of turbinalia, and osseous disorganization. The incidence of cysts in the thymus of females at LD and interstitial thickening of lung in males at LD were reversible. Treatment resulted in follicular atrophy (B cell) of lymph nodes at HD, atrophic ovary at HD, and spermiogenic disturbance in testes at LD. Treatment-related changes in skin were hair follicle regression at HD and decreased thickness of dermis at MD. Most toxicities in the 52-week dog study were due to typical glucocorticoid steroid effects of the drug. However, because of the incidences of chondrosis and osteofibrosis in the maxilloturbinates of nasal cavity of turbinalia, there was no clear NOAEL in this study. The target organs of toxicity were adrenal, lung, thymus, nose, lymph node, skin, testis, and ovary.

In a 4-week inhalation study in dogs with MDI (CFC) formulation, treatment (20, 60, and 180 $\mu\text{g}/\text{kg}/\text{day}$) resulted in decreased plasma cortisol levels at all doses, an increase in relative weight of spleens at all doses, and incidence of alveolar microhemorrhage at MD. The NOAEL was 180 $\mu\text{g}/\text{kg}/\text{day}$ and target organs of toxicity were lung, spleen, and adrenals. In a 26-week inhalation study with MDI (CFC) in dogs, treatment (2.5, 10, and

40 µg/kg/day) resulted in decreased plasma cortisol levels at LD, and an increase in the weights of thymus at lower doses (LD and MD) but a decrease at high dose (HD) was not explained. The NOAEL was 40 µg/kg/day. The target organs of toxicity were adrenal and thymus. Deposition factor was not considered in the calculation of dose. Thus, the dose could be over estimated as compared to other dog studies with DPI formulation.

**APPEARS THIS WAY
ON ORIGINAL**

GENETIC TOXICITY

In Vitro tests:

Bacterial Reverse Mutation (Ames) test.

Byk Gulden Study 107E/94, 20 January, 1993, Vol. C2.13

Study Dates: 11 April, 1990 to 10 June, 1990

Testing Lab: _____

Test Article: Ciclesonide (Batch #1-44).

GLP: The study was accompanied by a signed GLP statement.

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Method: The drug was tested in bacterial strains *Salmonella typhimurium* (TA 1535, TA 100, TA 1537, TA 98) with and without S9 (derived from liver homogenates from Aroclor 1254-treated rats). The bacterial cultures (in triplicates) were incubated with 0 (no add control), 0 (solvent control i.e. DMSO, 100 μ L/plate), 0.05, 0.158, 0.5, 1.58, and 5.0 mg per plate of test article for a period of 48 hours. Two independent experiments were conducted to determine reproducibility of the assay. The positive controls were:
With S-9 mix: 2-aminoanthracene (2 μ g/mL), benzo(a)pyrene (5 μ g/plate);
Without S-9 mix: sodium azide (2 μ g/plate), 2 nitrofluorene (1 μ g/plate). Negative controls were untreated and solvent treated cultures. A test is considered positive if the increase in the reversion rate in two independent assays is at least two-fold over the value of negative control and is dose dependent.

Results: Treatment of bacterial cultures with Ciclesonide did not result in an increase in mutation frequencies with or without S-9. Positive control yielded a typical result. Therefore, Ciclesonide was non mutagenic in the Ames test.

Chromosomal Aberration in Human Lymphocytes
Byk Gulden Study 111/94, 30 June, 1994, Vol. C2.13

Study Dates: 28 March, 1994 to 30 June, 1994

Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Hamburg, Germany

Test Article: Ciclesonide (Batch GU01/210A)

GLP: The study was accompanied by a signed GLP statement.

Method: Asynchronous population of lymphocytes was treated with Ciclesonide (in 1% DMSO) in the presence and the absence of metabolically active liver homogenates from Aroclor 1254-induced rats (S9 mixture). The dosing range was chosen from an exploratory study with 5 different drug concentrations ranging from 1 to 200 µmol/L. In the exploratory study, in the absence of S9, mitotic indices were reduced to 22% and 4% (at 100 and 200 µmol/L) compared to the lowest concentration (1 µmol/L); however, in the presence of S9, mitotic was reduced to 28% compared to 1 µmol/L. Lymphocyte cultures (in duplicates) were exposed to 0 (negative control), 1, 10, 50, and 75 µmol/L (without S9 mix and a treatment time of 24 h) and 10, 50, 100, and 150 µmol/L (with S9 mix and 4 h treatment) of drug; the cultures containing S9 were continued for another 20 hours in medium free of S9. Cells in all the cultures were harvested at 24 hours, stained and scored for structural chromosomal aberrations. The experiment was repeated with drug concentrations 10, 50, 100, and 150 µmol/L treated for 4 and 24 hours (cultures with and without S-9, respectively). Methyl methanesulfonate (125, 175, 250 µmol/L) and cyclophosphamide (10, 20 µmol/L)-treated cultures served as positive controls. Cultures treated with 1% DMSO served as negative controls. One hundred metaphases per culture were examined for achromatic lesions, chromatid and isochromatid breaks, and exchange aberrations.

The clastogenic potential of Ciclesonide was evaluated by an increase in the percentage of cells showing structural chromosomal aberrations. A response was considered positive if it resulted in a reproducible and concentration dependent increase in the aberration frequency over that in negative controls.

Result: Ciclesonide did not induce chromosomal aberrations in human lymphocytes and, therefore, was non-clastogenic. Positive control yielded a typical result.

CHO/HGPRT Mammalian Mutation Assay
Byk Gulden Study 209/95, 18 December 1995, Vol. C2.14

Study Dates: 18 October, 1995 to 18 December, 1995

Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Hamburg, Germany

Test Article: R-Ciclesonide (Batch MS181)

GLP: The study was accompanied by a signed GLP statement.

Method: The mutagenic potential of Ciclesonide was assessed in V79 Chinese hamster lung cells using HGPRT (or resistance to 6-thioguanine) as a marker. The cells were exposed to the test substance in the presence as well as absence of S9 (metabolic activation system from Aroclor 1254 pre-treated rats) for 4 hours. Doses for main study were based on preliminary dose ranging studies which showed 10% survival at top dose (150 $\mu\text{mol/L}$). Two independent experiments were conducted with following drug concentrations: Without S9: 50, 75, 90, 100, and 125 $\mu\text{mol/L}$; With S9: 100, 120, 130, and 140 $\mu\text{mol/L}$. Four cultures/group for treatment groups and 8 cultures/group for control were tested. Ethyl methane-sulfonate (8000 $\mu\text{mol/L}$) was used as a positive control "without metabolic activation" while 9, 10-Dimethyl-1,2-benzanthracene (DMBA dissolved in DMSO; final concentration in growth medium: 60 $\mu\text{mol/L}$) served as positive control "with metabolic activation." The criteria for a positive control for this test were: a reproducible concentration-related increase in mutant frequency and, reproducible and statistically significant positive response for at least one of the test substance concentrations.

Result: R-Ciclesonide was non-mutagenic under the conditions of this assay. Positive control yielded a typical result.

***In vitro* Micronucleus Test (V79 cells)**
Byk Gulden Study 80/97, 30 April 1997, Vol. C2.14

Study Dates: 24 February, 1997 to 30 April, 1997

Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Hamburg, Germany

Test Article: Ciclesonide (Batch MS181).

GLP: The study was accompanied by a signed GLP statement.

Method: The concentrations used in this study were based on those used in HGPRT Mammalian Mutation study (205/95). Two independent experiments were performed; however, only single replicate cultures was used for each treatment. Five to 100 µg/mL of drug dissolved in DMSO (1% in culture medium) was used. Negative control consisted of 1% DMSO in culture medium. There were two positive control groups: without S9: 0.0087 and 0.0117 µg Colcemid/mL; with S9: 3.16 µg Cyclophosphamide/mL. Treatment period was 21 hours for cultures without S9 and 3 hours with 18 hour recovery period for cultures with S9. One thousand cells were counted for incidence of micronuclei per cell culture (experimental group).

The criteria for a positive control for this test were: incidence of micronuclei should be 3 times higher than the concurrent control; clear dose-response relationship; and reproducibility of effects.

Results: Ciclesonide was non-clastogenic under the conditions of this assay. Positive control yielded a typical result.

***In Vivo* tests:**

Mouse micronucleus tests.
Byk Gulden Studies, Vol. C2.14

Study Numbers ⇒	100/95	161/95	161/96	75/96
Study Dates	13 Feb - 15 Jun 1995	21 Jul - 29 Sep 1995	20 Sep - 26 Nov 1996	7 Mar - 17 Jun 1996
Testing Lab	Byk Gulden	Byk Gulden	Byk Gulden	Byk Gulden
Ciclesonide				
Batch No.	MS181	MS181	MG225C	MS181
GLP	EC	EC	EC	EC

EC = GLP requirements of European Community were followed.

Method: Four independent micronucleus tests (1, 2, 3, 4) were performed; however, only two (test 1 and 4) of these studies are relevant since in other two studies (2 and 3), the highest dose used was not sufficiently high. Ciclesonide (25-2000 mg/kg; See Table on next page for doses given in individual tests) in aqueous solution with 0.04 g Tween 80/kg and 0.08 g Keltrol/kg was administered orally. Dosing Volume was 20 mL/kg (Tests 1, 2) or 10 mL/kg (Tests 3, 4). Negative Control consisted of H₂O with 0.04% Tween 80/kg and 0.08 g Keltrol RD/Kg. Positive Control used was Cyclophosphamide (25 mg/kg). Bone marrow samples were collected at 24 and 48 hours. Budesonide and Dexamethasone (25-1000 mg/kg) were also studied. Doses of all three drugs in Test 1 and 4 were sufficiently high.

Two thousand polychromatic erythrocytes (PE) from each animal were evaluated for the presence of micronuclei. In addition, the observed number of micro nucleated normochromatic erythrocytes (NE) was also recorded and PE/NE ratio determined. Criterion for a positive response is an occurrence of 2 significant responses from different sampling times in the same experiment.

Results: As shown in the Table on the following page, data showed that treatment with Ciclesonide resulted in formation of micronuclei as reflected by: (a) an increase in the proportion of MPEs in the treatment groups over that in negative control; (b) a dose-related increase in the proportion of MPEs. Thus, it would seem that Ciclesonide is clastogenic in this test. However, this positive result (micronucleus test) for Ciclesonide

is as positive as that seen for other glucocorticoid steroids (Budesonide and Dexamethasone); See Table.

GENETIC TOXICITY: MOUSE MICRONUCLEUS TESTS

	Micronucleated Polychromatic Erythrocytes/2000 cells			
Treatment Group and Oral Dose (mg/kg)	CICLESONIDE		OTHER STEROIDS	
TEST 1	24 hours	48 hours		
500	2.8	5.1		
1000	4.7	6.5		
2000	5.6	3.8		
Negative Control	2.0	2.4		
Positive Control	36.1			
TEST 2	24 hours	48 hours		
25	3.4	3.0		
75	3.9	3.1		
150	3.4	4.1		
Negative Control	3.9	1.8		
Positive Control	20.0			
TEST 3	24 hours	48 hours		
0.25	1.3	1.0		
2.50	2.0	3.0		
25.00	2.6	2.5		
Negative Control	1.6	3.0		
Positive Control	33.8			
TEST 4	24 hours	48 hours	DEXAMETHASONE	
25	2.8	1.9	24 hours	48 hours
150	2.7	2.8	4.6	3.4
1000	3.8	2.8	4.3	4.2
Negative Control	1.3	2.3	3.6	4.2
Positive Control	32.4			
			BUDESONIDE	
25			24 hours	48 hours
			3.7	3.0

150		3.4	3.4
1000		4.0	4.7

**APPEARS THIS WAY
ON ORIGINAL**

SUMMARY OF GENETIC TOXICITY

At the dose ranges used in these studies, Ciclesonide was neither genotoxic (Ames battery, CHO/HGPRT mammalian mutation assay) nor clastogenic in *in vitro* chromosomal aberrations in human lymphocytes and *in vitro* micronucleus test; however, it was as clastogenic in *in vivo* mouse micronucleus tests as other approved steroids such as Dexamethasone and Budesonide.

REPRODUCTIVE TOXICITY

Rat: Segment-II Oral Toxicity

Byk Gulden Study 109/95, 02 August 1995, Vol. C2.14

Study Dates: 12 August, 1994 to 02 August, 1995

Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Hamburg, Germany

Test Article: Ciclesonide (Batch MS181).

GLP: Signed GLP statement attested to compliance with GLP of EC;
compliance to GLP of U.S.FDA was not indicated.

Species/Strain: Rat (Sprague Dawley).

Animals: 92 females; 21-26 females/group.

Route: Oral by stomach tube

Dosage: 100 µg/kg/day (LD); 300 µg/kg/day (MD); 900 µg/kg/day (HD). Dosing volume=4 mL/kg.

Duration of Exposure: Day 6 to Day 15 after mating.

METHODS

Observations: F₀ Generation:

1. Adult Females:

Clinical Signs and Mortality: Daily.

Body Weights: On Day 0, daily from Day 6 to Day 15, and on Day 20.

Food Consumption: Daily.

2. Litter data and fetal examinations for animals sacrificed on Day 20 of Pregnancy:

Gravid uterus weight, implantation rate, pre-implantation loss, post implantation loss, number of living fetuses/dam were studied

Observations: F₁ Generation:

Behavior and appearance, determination of sex, body weight changes, visceral and skeletal changes.

RESULTS

1. Adult Females:

Clinical Signs: No toxicologically significant treatment-related effects.

Mortalities: There were no mortalities.

Body Weights: Treatment resulted in 15% decrease in body wt. gains (HD).

Food Consumption: No toxicologically significant treatment-related effects.

2. Dams at Autopsy:

Gravid Uterus Weight: No toxicologically significant treatment-related effects.

Implantation Rate and Pre- and Post-implantation losses: No toxicologically significant treatment-related effects.

Number of Living Fetuses: No toxicologically significant treatment-related effects.

3. Fetuses:

Behavior and Appearance: No toxicologically significant treatment-related effects.

Body Weights: No toxicologically significant treatment-related effects.

Skeletal and Visceral Changes: No toxicologically significant treatment-related effects.

Rabbit: Segment-II Oral Toxicity
Byk Gulden Study 106/95, 27 July 1995, Vol. C2.14

Study Dates: 11 October, 1994 to 14 December, 1994

Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Hamburg, Germany

Test Article: Ciclesonide (Batch MS181) solution in PEG 400.

GLP: Signed GLP statement attested to compliance with GLP of EC;
compliance to GLP of U.S. FDA was not indicated.

Species/Strain: Rabbit (Little Russian, Himalayan).

Animals: 56 Females; 12-14/group.

Route: Subcutaneous application. In a preliminary study, doses between 50 and 2000 $\mu\text{g}/\text{kg}/\text{day}$ resulted in 50 to 100% loss in food consumption hence, the sponsor decided to administer drug via subcutaneous route. When 100, 500, and 1000 $\mu\text{g}/\text{kg}/\text{day}$ of the drug were administered (s.c.), the dam receiving 1000 $\mu\text{g}/\text{kg}/\text{day}$ was not pregnant; Under 500 $\mu\text{g}/\text{kg}/\text{day}$, the dam showed total abortion.

Dosage: 25 $\mu\text{g}/\text{kg}/\text{day}$ (LD); 100 $\mu\text{g}/\text{kg}/\text{day}$ (MD); 400 $\mu\text{g}/\text{kg}/\text{day}$ (HD). Dosing
Volume: 0.2 mL/kg.

Duration of Exposure: Day 6 to Day 18 after mating.

METHODS

Observations: F₀ Generation:

1. *Adult Females:*

Clinical Signs and Mortality: Daily.

Body Weights: On Day 0, daily from Day 6 to Day 18, and on Day 29.

Food Consumption: Daily.

2. *Litter data and fetal examinations for animals sacrificed on Day 29 of Pregnancy:*

Gravid uterus weight, implantation rate, pre-implantation loss, post implantation loss, number of living fetuses/dam were studied.

Observations: F₁ Generation:

Behavior and appearance, determination of sex, body weight changes, visceral and skeletal changes.

RESULTS

1. Adult Females:

Clinical Signs: Incidence of blood on bedding was drug-related [Controls 3 (days 20-28); LD 3 (days 16-28); MD 10 (days 21-28); and HD 13 (days 15-28)].

Mortalities: There were no mortalities.

Body Weights: No toxicologically significant treatment-related effects.

Food Consumption: No toxicologically significant treatment-related effects.

2. Dams at Autopsy:

Gravid Uterus Weight: No toxicologically significant treatment-related effects.

Implantation Rate and Pre- and Post-implantation losses: No toxicologically significant treatment-related effects on implantation rate or pre-implantation losses. Post-implantation loss was drug-related (Control 27.1%, LD 18.5%, MD 44%, HD 100%). Thus, the drug was embryocidal at MD.

Number of Living Fetuses: There were no living fetuses in HD group. No toxicologically significant treatment-related effects at LD and MD.

3. Fetuses:

Behavior and Appearance: No toxicologically significant treatment-related effects.

Body Weights: The litter weights were significantly reduced at MD (52%). The fetal weights per litter were significantly reduced in a dose dependent manner (LD 10%, MD 35%). Therefore, the drug was fetotoxic at LD.

Skeletal and Visceral Changes: The drug was teratogenic at 25 µg/kg/day:

- **25 µg/kg/day:**
 - Two fetuses with cleft palates;
 - Three fetuses with 6 acampsias (=inflexibility of a joint);
 - Largeness of fontanelle in 18 fetuses;
 - Pergameneous skin in 2 fetuses;
 - One Microtia;
 - Two-exencephaly;
 - One ablepharia (cyptophthalmos=skin being continuous over the eye ball without any indication of the formation of eyelids);
 - One umblical hernia;
 - One dysmelia (=defect of excessive development or reduction deformity).

- **100 µg/kg/day:**
 - A significantly higher incidence of acampsia (flexure of fore and hind paws) in 37 fetuses
 - Cleft palate in 22 fetuses,
 - Largeness of fontanelle (a soft spot remaining in the incompletely ossified skulls) in 27 fetuses;
 - Pergameneous skin in 7 fetuses;
 - One microtia (gross hypoplasia or aplasia of the pinna of the ear, with a blind or absent acoustic meatus);
 - One cranial meningocele (hernial protrusion of the meninges through a bony defect);
 - Two exencephaly (incidence of an imperfect cranium in which brain lies outside of the skull);
 - One brachydactyly (shortness of fingers and toes);
 - One umblical hernia.

- **400 µg/kg/day:** 100% postimplantive fetus loss due to resorption or abortion; no morphological features studied.

SUMMARY OF REPRODUCTIVE TOXICITY

In the Segment-II oral study in rats, treatment with drug (100, 300, and 900 $\mu\text{g}/\text{kg}/\text{day}$) resulted in 15% decrease in bodyweight gains (HD) in the mother but no toxicologically significant treatment-related effects on fetuses. The drug was neither embryo/fetotoxic nor teratogenic.

In a Segment-II (subcutaneous) study in rabbits, treatment (25, 100, and 400 $\mu\text{g}/\text{kg}/\text{day}$) resulted in post-implantation loss and reduced litter weight at 100 $\mu\text{g}/\text{kg}/\text{day}$ and above. There were no living fetuses in HD group. Fetal weight was reduced at 25 $\mu\text{g}/\text{kg}/\text{day}$ and above. Treatment-related skeletal and visceral changes in the fetuses are cleft palates, acampsias, largeness of fontanelle, pergameneous skin, microtia, exencephaly, ablepharia, umbilical hernia, dysmelia (=defect of excessive development or reduction deformity), cranial meningocele, exencephaly, brachydactyly. The drug was teratogenic and fetotoxic at 25 $\mu\text{g}/\text{kg}/\text{day}$.

SPECIAL TOXICITY

Guinea Pig: Immunostimulation: Skin Sensitization Byk Gulden Study 122/94, 19 August 1994, Vol. C2.13

Study Dates: 30 May, 1994 to 24 June, 1994
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: 10% Ciclesonide in 96% ethanol.
GLP: The study was accompanied by a signed GLP statement.

Method: This "Guinea Pig Maximization Test" was conducted on 15 female guinea pigs (Strain: Dunkin-Hartley). The animals were divided in two groups: a negative control (Vehicle only) group with 5 animals and a test group with 10 animals.

First Induction: On Day 2, a total of 6 intradermal injections of 0.1 mL were given over the shoulder area to each animal. Two injections contained FREUND's adjuvant alone, two injections were made up of adjuvant mixed with the vehicle (negative control group) or with the test compound (Test group), and two injections contained either vehicle or test compound alone. On day 3-5, the animals were examined for the skin reaction to the injections.

Second Induction: On Day 9, the animals were treated topically over the shoulder area with either the vehicle (negative control group) or test compound (Test group). The vehicle solution or test mixture were placed on aluminum FINN-Chambers which were then applied to the skin and left in place for 24 hours. The skin was examined on Day 11 for any reaction.

Challenge: On Day 23, all animals (both groups) were treated topically on one side with the drug using method used for second induction. Dressing and chamber were left in place for 24 hours and then removed. On Days 25 and 26, the skin reaction was evaluated.

Result: In 1 Control and 3 treated animals, a skin reaction was noted 24 hours after challenge; however, after 48 hours after the challenge procedure, skin of all animals was normal. Thus, treatment with Ciclesonide did not reveal sensitization potential under experimental conditions.

OVERALL SUMMARY AND EVALUATION

b(4)

Pharmacology: R-Ciclesonide is a prodrug that is rapidly converted to an active metabolite. The drug exhibited immunosuppressive properties in *in vitro* models. It had anti-inflammatory activity in mice and rats. The drug had pharmacodynamic activity relevant to proposed indication in rats. R epimer, _____ S epimer. R-Ciclesonide or its metabolite were more potent than Budesonide.

Safety Pharmacology: Ciclesonide had no significant effects on CNS in mice and rats and cardiovascular and respiratory system in cats.

Absorption, Distribution, Metabolism, and Excretion: The oral bioavailability of the drug in dogs was about two-fold of that in rats. This was reflected by higher C_{max} in dogs (p.o.) than that in rats (p.o.). The $T_{1/2}$ was shorter in rat compared to dog. The T_{max} in rats and dogs were comparable for oral route. In dog, inhalation administration of the drug resulted in high C_{max} indicating high bioavailability. In rat, the drug was distributed in the following order:

i.v.: Lung>Heart>thyroid >kidney >liver>G.I. Tract>adrenals>thymus; **p.o.:** G.I. Tract>liver >kidney>thyroid >adrenal, spleen, skin>lung>thymus; **i.t.:** Trachea>Thyroid>G.I. tract>lung>Eye>thymus.

The drug was more rapidly metabolized to major metabolite (M_1) in lung homogenates from rat than those from dog. In liver homogenates from rats, there was marked sex difference in the metabolism of the drug; the drug metabolized about 8-times faster in females than in males. In rat liver microsomes (S9 fraction), the drug was rapidly metabolized. In dog liver homogenates (both sexes), the metabolism of the drug was quite fast. In homogenates from mouse skin, rate of metabolism was slower than that in rat lung homogenates but faster than dog lung homogenates. Minor metabolites were M_2 , M_3 , M_4 , and M_5 . In both rats and dogs, most drug was excreted via feces (p.o. or i.v.).

Toxicology:

a) Single Dose: In single dose lethality (i.p.) studies in mice and rats, minimal lethal dose was 200 mg/kg and the target organs of toxicity were thymus, spleen, and adrenal. Oral dose was well tolerated. No mortality was reported in rats and mice at oral doses up

to 2000 mg/kg. The target organs of toxicity in rats were spleen and adrenals. The target organs of toxicity in mice could not be identified.

b) **Multiple Dose:** In rats, a 4-week inhalation administration of DPI formulation of the drug resulted in NOAEL of 50.5 µg/kg/day and thymus was the target organ of toxicity. However, when the drug was given to rats for 26 weeks at doses of 16.5 to 166.0 µg/kg/day, there was no clear NOAEL. The target organs of toxicity were thymus, mesenteric lymph node, lung, and mammary gland. These findings suggest duration dependent toxicity of the drug in rats.

In rats, the MDI formulation (with HFA and ethanol) given for 4 weeks in a dose ranging study, resulted in a NOAEL of less than 184 µg/kg/day with thymus being the target organ of toxicity.

In dogs, a 4-week inhalation study with DPI formulation of the drug resulted in NOAEL of 50 µg/kg/day for males and 15 µg/kg/day for females implying gender difference in toxic effects. The target organs of toxicity were adrenal, lung, and thymus. In a 52-week inhalation toxicity study in dogs with DPI formulation at doses of 18 to 92 µg/kg/day, NOAEL could not be established thus, implying duration dependent toxicity of the drug in dogs. The target organs of toxicity were adrenal, lung, thymus, nose, lymph node, skin, testis, and ovary.

In dogs, treatment with MDI formulation (with CFC) of the drug for 4 and 26 weeks resulted in NOAEL of 180 µg/kg/day and 40 µg/kg/day, respectively. The target organs of toxicity were adrenals, lung, and spleen in the 4 week study and adrenal and thymus in the 26 week study. Here again, duration dependent toxicity of the drug was evident. Deposition factor was not considered in the calculation of dose. Thus, the dose could be over estimated as compared to other dog studies with DPI formulation.

Treatment with Ciclesonide resulted in typical glucocorticoid steroid effects mainly on thymus, spleen, adrenal, mammary gland, testis, ovary, and lymph node with few exceptions in which higher doses resulted in an exaggerated pharmacologic effect and local toxic effects in the respiratory tract (lung, nose, etc.).

It should be noted that proposed clinical formulation is MDI with HFA and ethanol. The only study that is available with this formulation is a 4 week dose ranging toxicity study in rats. There was no toxicity study of the proposed formulation available in a non rodent species. Safety of an NME should be evaluated in 2 species prior to initiation of a clinical study and that animal studies should be conducted using same formulation (especially for

new propellants) as that proposed to be used in the clinical study. Furthermore, additional study to bridge the chronic toxicity data of DPI to that of the proposed formulation is needed.

Genetic Toxicity: Ciclesonide was neither genotoxic (Ames battery, CHO/HGPRT mammalian mutation assay) nor clastogenic in *in vitro* chromosomal aberrations in human lymphocytes and *in vitro* micronucleus test; however, it was clastogenic in an *in vivo* mouse micronucleus test. However, other approved steroids such as Dexamethasone and Budesonide exhibited similar finding in this assay.

Reproductive Toxicity: Ciclesonide was neither embryo/feto-toxic nor teratogenic in rats at oral doses up to 900 $\mu\text{g}/\text{kg}/\text{day}$. In rabbits, it was fetotoxic and teratogenic at subcutaneous dose of 25 $\mu\text{g}/\text{kg}/\text{day}$ and embryocidal at 100 $\mu\text{g}/\text{kg}/\text{day}$.

Special Toxicity: In guinea pig skin sensitization study, treatment with Ciclesonide did not reveal sensitization potential under the stated experimental conditions.

Safety of HFA-134a: The Excipient HFA-134a has been fully evaluated preclinically in a DMF () and the sponsor has enclosed a letter of authorization from _____ who is one _____ with legal rights for the data contained in the DMF.

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Safety of Ethanol: _____ percent ethanol has been used in other approved inhalation products.

Clinical Dose: The sponsor proposed a clinical study of one year duration available using the MDI formulation (with HFA and ethanol) and doses: 800 $\mu\text{g}/\text{day}$ or 16 $\mu\text{g}/\text{kg}/\text{day}$ (3 months) and 1600 $\mu\text{g}/\text{day}$ or 32 $\mu\text{g}/\text{kg}/\text{day}$ (9 months). The preclinical data do not support the proposed clinical trial because a clear NOAEL could not be determined in relevant inhalation toxicity studies in rat (26 week) and dog (52 weeks). In addition, both animal studies were conducted using the dry powder formulation and no completed preclinical studies are available using the MDI formulation (with HFA and ethanol).

The MDI formulation of the drug (with HFA and ethanol) has been given to humans for 1 week only. However, the sponsor has proposed a clinical study of 12 months duration. Therefore, this clinical study should be put on hold until the safety of the drug is established in preclinical studies.

For change of formulation to new HFA (MDI), preclinical studies to bridge from DPI to MDI formulation are needed. For the drug applications submitted to Division of Pulmonary Drug Products, 2 week studies in 2 species (1 rodent and 1 non rodent) and a 3 month study in the most appropriate species are generally recommended. For the drugs for which large amount of human data are available, the above bridging studies are needed for NDA only. However, in case of Ciclesonide, human data are minimal and, therefore, toxicity studies of the proposed formulation in two species with similar duration to that proposed are required prior to the clinical trial.

The sponsor has conducted one 4 week toxicity study in rat using MDI-HFA formulation (report pending). In a teleconference with the review team, the sponsor indicated that another 4 week toxicity study (with MDI-HFA formulation) in dog is in progress. If data from these two studies can establish safety of the drug, a clinical study of 4 weeks duration can be permitted. The sponsor should conduct a 3 month toxicity study in the most appropriate species prior to exceeding 4 week duration of clinical study.

If data from the above preclinical studies allow bridging between two formulations and NOAEL in 6 month rat and 12 month dog studies (both with DPI) can be established, then no additional animal studies may be necessary.

RECOMMENDATION

We found it was not reasonably safe to allow the clinical trial from a preclinical standpoint. The sponsor has requested that the IND should be placed in inactive status. The Division has recommended the sponsor for a meeting. The above-mentioned comments and recommendation should be conveyed to the sponsor as shown in the draft letter to the sponsor.

Points discussed with Medical Officer: Ciclesonide was teratogenic at 25 µg/kg/day and embryocidal at 100 µg/kg/day in Rabbit Segment-II Reproductive Toxicity Study. This information should be added in the future Informed Consent section of the Clinical Protocol(s).

Information for Future Investigator's Brochure/Informed Consent: Ciclesonide is teratogenic at 25 µg/kg/day and embryocidal at 100 µg/kg/day in Rabbit Segment Segment-II Reproductive Toxicity Study.

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 ✓ Deliberative Process (b5)

File Name: N:\IND\53391\PHARM\97-05-23.REV

Satish C. Tripathi, Ph.D.
Pharmacology/Toxicology Reviewer

Original IND
C.C. HFD-570/Division File
HFD-570/Joseph Sun, Team Leader, Pharmacology/Toxicology
HFD-570/Martin Himmel, Deputy Division Director
HFD-570/Richard Nicklas, Medical Reviewer
HFD-570/Lindsay Cobbs, Project Manager
HFD-570/Satish Tripathi, Pharmacology/Toxicology Reviewer

ATTACHMENT 2

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Addendum Original, Review No. 2

IND Number: 53,391

Serial Number(s): 000

Date(s) of Submission: Letter Date: May 23, 1997
CDER Stamp: June 03, 1997

Information to be Conveyed to Sponsor: Yes (X), No ()

Reviewer: Satish C. Tripathi, Ph.D.

Date Review Completed: September 05, 1997

Sponsor: Byk Gulden Lomborg Chemische Fabrik
GmbH, Postfach 10 03 10, 78403
Konstanz, Germany (Dr. Petra
Willersinn-Kern:
Tel: 011-49-7531-84-2837).

Sponsor (U.S. Representative): Altana Inc., 60 Baylis Road, Melville,
NY 11747 (Miss Virginia Carman:
516-454-7677 Extension 2091).

Manufacturer: _____ **hb(4)**

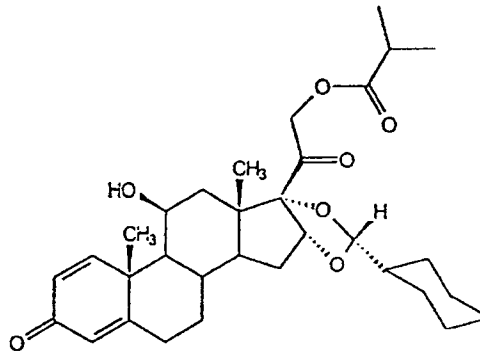
Drug Name: Primary: Ciclesonide
Other Names: Byk Gulden B9207-015

Chemical Name: [11 β , 16 α (R)]-16, 17-
[Cyclohexylmethylene) bis(oxy)-11-
hydroxy-21-(2-methyl-1-
oxopropoxy)pregna-1, 4-diene-3, 20-
dione.

CAS Number:

141845-82-1

Structure:



Molecular Weight and Formula:

540.7; C₃₂H₄₄O₇

Related INDs/NDAs/DMFs:

DMF — Toxicology testing of HFA-134a
(MDI Propellant) —

Class:

Glucocorticoid Steroid.

Indication:

Mild to moderate chronic asthma.

Clinical Formulation:

White to off-white powder available as MDI that delivers 100, and 200 µg (ex valve) per puff. Other ingredients: (w/w) propellant HFA-134a and (w/w) ethanol.

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Route of Administration:

Inhalation (via MDI).

Proposed Clinical Protocol:

Objective: To study: (i) the effect of two doses of Ciclesonide vs. placebo on pulmonary function, asthma symptoms, and concomitant use of the β_2 -agonist (albuterol) in patients with chronic asthma; (ii) the long-term safety of Ciclesonide; and (iii) the long-term effect of Ciclesonide on pulmonary function and number of exacerbations.

Dose:

Double-blind segment: 200 or 800 $\mu\text{g}/\text{day}$ (4 Puffs @ 50 or 200 $\mu\text{g}/\text{puff}$).

Open label extension:

Patients without asthma exacerbation: 800 $\mu\text{g}/\text{day}$ (4 puffs once daily)

Patients with asthma exacerbation: 800 $\mu\text{g}/\text{day}$ (4 puffs once daily) or 1600 $\mu\text{g}/\text{day}$ (4 puffs twice daily).

Later phase of open label extension:

200 $\mu\text{g}/\text{day}$ (1 puff @ 200 $\mu\text{g}/\text{puff}$); 400 $\mu\text{g}/\text{day}$ (2 puffs @ 200 $\mu\text{g}/\text{puff}$), 800 $\mu\text{g}/\text{day}$ (4 Puffs @ 200 $\mu\text{g}/\text{puff}$) or 1600 $\mu\text{g}/\text{day}$ (4 Puffs @ 200 $\mu\text{g}/\text{puff}$, bid). For a 50 kg individual, the highest dose translates to 16 $\mu\text{g}/\text{kg}/\text{day}$ (3 months) to 32 $\mu\text{g}/\text{kg}/\text{day}$ (9 months).

Frequency: Daily.

Duration: 12 weeks for double blind segment; 40 weeks for open label.

Patient population: 240 patients (age: 18-70 years; either sex) with chronic asthma.

Previous Submission, Review Date and Reviewer: 05/23/97; 08/03/97; Satish C. Tripathi, Ph.D.

Studies Reviewed in this IND: This is an addendum review for those studies not

previously reviewed as indicated in the original IND review of 08/03/97.

TOXICOLOGY
1. Mice: 13-wk Oral Toxicity, Vol. C2.10. 2. Rat: 4-wk Oral Toxicity, Vol. C2.6. 3. Rat: 26-wk Oral Toxicity, Vol. C2.12. 4. Rat: 4-wk Subcutaneous Toxicity, Vol. C2.12. 5. Rat: 26-wk Subcutaneous Toxicity, Vol. C2.13. 6. Dog: 4-wk Oral Toxicity, Vol. C2.7. 7. Dog: 2-wk Intravenous Toxicity, Vol. C2.5.
SPECIAL TOXICITY
1. Dog: Hemolytic potential following short-term intravenous administration, Vol. C2.13. 2. Guinea Pig: Primary irritation after single dose epicutaenous administration, Vol. C2.13. 3. Rabbit: Local Toxicity after a single intravenous, paravenous, or intraarterial administration, Vol. C2.13. 4. <i>In Vitro</i> Erythrocyte Stability test with rat, dog, and human blood, Vol. C2.13.

Studies Previously Reviewed: See Original IND review of 08/03/97.

PHARMACOLOGY
Pharmacodynamics <i>in vivo</i> and <i>in vitro</i> ; Safety Pharmacology.
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION
Absorption, distribution, metabolism in rats and dogs.
TOXICOLOGY
1. Mice: Acute Toxicity (i.p.) 2. Mice: Acute Toxicity (p.o.) 3. Rat: Acute Toxicity (i.p.) 4. Rat: Acute Toxicity (p.o.) 5. Rat: 4-wk Inhalation Toxicity with Dry Powder Formulation. 6. Rat: 4-wk Dose Ranging Inhalation Toxicity with Metered-dose HFA-formulation. 7. Rat: 26-wk Inhalation Toxicity with Dry Powder Formulation. 8. Dog: 4-wk Inhalation Toxicity with Dry Powder Formulation. 9. Dog: 52-wk Inhalation Toxicity with Dry Powder Formulation. 10. Dog: 4-wk Inhalation Toxicity with Metered-dose CFC-formulation. 11. Dog: 26-wk Inhalation Toxicity with Metered-dose CFC-formulation.
REPRODUCTIVE TOXICITY
1. Rat: Segment II. 2. Rabbit: Segment II.
GENETIC TOXICITY
<i>In Vitro</i> tests: 1. Bacterial Reverse Mutation (Ames) test. 2. Chromosomal aberration in human lymphocytes. 3. HPRT test (V79 cells). 4. Micronucleus test with V79 cells. <i>In Vivo</i> tests: 1. Mouse micronucleus tests.
SPECIAL TOXICITY
1. Guinea Pig: Skin sensitization study.

Studies Not Reviewed: Due to complete study report not being available, the following study is not reviewed: _____

b(4)

Note: Portions of this review were excerpted directly from the sponsor's submission.

TOXICOLOGY

Mice: 13-wk Oral Toxicity

Byk Gulden Study 185/95, 08 August, 1996, Vol. C2.10

Study Dates: 11 July, 1995 to 11 October, 1995

Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.

Test Article: Ciclesonide solution in polyethylene glycol 400.

GLP: Signed GLP statement was not included.

METHODS

Species/Strain: Mice/B6C3F1

Animals: 40/Sex; 10/Sex/group.

Route: Oral with gastric canula.

Dosage: 0 (Vehicle Control); 50 µg/kg/day (LD); 150-900 µg/kg/day (HD-1); 450 µg/kg/day (HD-2). Due to normal bodyweight gain in all groups until the end of 4th study week, the dose 150 µg/kg/day was raised to 900 µg/kg/day. Dosing Volume: 4 mL/kg.

Duration of Exposure: 13 weeks.

Clinical Observations: Daily.

Body Weights: Days -1, 1; twice a week for 4 weeks; and once a week thereafter.

Food Consumption: Day 1; twice a week for 4 weeks; and once a week thereafter.

Hematology: Week 13.

Clinical Chemistry: Not performed.

Urinalysis: Not performed.

Drug Levels: Not determined.

Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortalities: There were no mortalities.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in decreased bodyweight gain in females (LD: 12%, HD-2: 25%, HD-1: 37%).

Food Consumption: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Organ Weights: No toxicologically significant treatment-related effects.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Treatment resulted in the incidence of follicular atrophy of spleen (HD-1: ♂: 8/10; ♀: 1/9).

In the absence of signed GLP statement and unavailability of data on clinical chemistry, urinalysis, and drug plasma levels, this study cannot be considered valid for safety determination. Thus, NOAEL cannot be determined at this time. The sponsor should be asked to provide additional information.

APPEARS THIS WAY ON ORIGINAL

Rat: 4-wk Oral Toxicity
Byk Gulden Study 76/94, 30 December, 1994, Vol. C2.6

Study Dates: 15 March, 1994 to 30 December
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: Ciclesonide solution in polyethylene glycol 400.
GLP: Signed GLP statement was included.

METHODS

Species/Strain: Rat (Sprague-Dawley).
Animals: 56/Sex; 10/Sex/group (Control and all treatment groups); 8/Sex/group (Recovery: Control and HD groups).
Route: Oral via gastric canula.
Dosage: 0 (Vehicle Control); 100 µg/kg/day (LD); 450 µg/kg/day (MD); 2000 µg/kg/day (HD). Dosing Volume: 4 mL/kg.
Duration of Exposure: 4 weeks.
Clinical Observations: Daily: immediately and 3, 6, and 24 hours after dosing.
Body Weights: Days -1 and 1 of dosing; twice weekly during treatment period and on days 30 and 57 (recovery groups only).
Food Consumption: Day 1 of dosing; twice weekly during treatment period and on days 30 and 57 (recovery groups only).
Ophthalmoscopy: Days -7, 28, and 55 (recovery groups only).
Electrocardiography: 4 hours post dosing on Day 21 (3 leads EKG).
Hematology: Days -6, 29, and 56 (recovery groups only).
Clinical Chemistry: Days -6, 29, and 56 (recovery groups only).
Urinalysis: Days 28/29, and 55/56 (recovery groups only).
Drug Levels: Not determined.
Vaginal Smears: Day 1-30 and 1-57 (recovery groups only).
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortalities: Death of 1 HD female was due to technical error (administration of drug into the lung).

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in decreased bodyweight gains (♂: HD 28%; ♀: MD 25%, HD 47%).

Food Consumption: Decreased food consumption (Day 21-27: 14%) was reported for HD females.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Electrocardiography: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: Treatment resulted in statistically significantly increased levels of ALT (σ : MD 10%, HD 25%; ♀ : MD 47%, HD 100%) and AST (σ : MD 18%, HD 16%; ♀ : MD 20%, HD 35%) and slightly decreased (but statistically significant) levels of K^+ (σ : HD 8%; ♀ : HD 9%) which were reversed in HD Recovery group. Increased levels of ALT were biologically significant.

Urinalysis: HD resulted in statistically and biologically significant decrease in urine K^+ (σ : 17%; ♀ : 16%).

Vaginal Smears: Treatment resulted in decreased number of estrus events/animal (HD 15%, Recovery HD 16%) in females.

Organ Weights: Treatment resulted in increased relative weights of heart (σ : HD 12%; ♀ : HD 17%) and brain (σ : HD 13%; ♀ : MD 13%, HD 23%) and decreased relative weights of spleen (σ : MD 10%, HD 10%; ♀ : HD 9%), adrenals (σ : HD 15%; ♀ : MD 11%, HD 14%), and thymus (σ : MD 16%, HD 44%; ♀ : MD 15%, HD 55%) which were reversed in the HD recovery group.

Gross Pathology: Incidence of thymus involution (σ : MD 2/10, HD 10/10, Recovery Control 2/8, Recovery HD 4/8; ♀ : Control 1/10, MD 2/10, HD 8/10, Recovery Control 2/8, Recovery HD 1/8) was drug-related.

Histopathology:

Histopathologic Findings

Organ	Finding	Incidence
Adrenals	Atrophy of adrenal cortex	♂: HD 7/10 ; ♀: HD 9/9
Thymus	Thymic atrophy	♂: C 5/10, LD 2/10, MD 2/10, HD 10/10; RC 4/8 RHD 4/8 ♀: LD 2/10, MD 2/10, HD 9/9; RC 2/8 RHD 1/8
Lymph Node, Mesenteric	Depletion of lymphocytes in the cortex	♀: HD (data not provided)
Mammary Gland	Alveolarization	♂: C 5/10, HD 8/10, RC 4/8, RHD 6/8; ♀: HD 3/9
Skin	Atrophy	♂: C 4/10, HD 6/10, RC 4/8, RHD 8/8; ♀: HD 7/9, RC 2/8, RHD 4/8
Tibia	Bone marrow: cell depletion	♂: HD 7/10; ♀: HD 1/9
	Disorganized epiphysis	♂: HD 3/10; ♀: HD 1/9, RHD 1/9
	Megakaryocytic degeneration	♂: C 1/10, HD 4/10, RC 2/8, RHD 2/8
	Hyperostosis	♀: HD 8/10, RHD 1/8

C=Vehicle Control; RC=Recovery Control; RHD=Recovery High Dose

NOAEL: Due to histologic findings at HD (see above), the MD (450 µg/kg/day) is the NOAEL.

Rat: 26-wk Oral Toxicity
Byk Gulden Study 223/95, 20 August, 1996, Vol. C2.12

Study Dates: 03 May, 1995 to 05 December, 1995
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: Ciclesonide solution in polyethylene glycol 400.
GLP: Signed GLP statement (EU Compliance) was included.

METHODS

Species/Strain: Rat (Wistar).
Animals: 96/Sex; 28/Sex/group (Vehicle Control, HD); 20/Sex/group (LD, MD).
Route: Oral via gastric canula.
Dosage: 0 (Vehicle Control); 80 µg/kg/day (LD); 360 µg/kg/day (MD); 1600 µg/kg/day (HD). Dosing volume: 4 mL/kg. The concentration of the HD dosing solution was 0.04% (Vehicle: PEG 400); LD and MD dosing solutions were prepared by diluting 0.04% stock with PEG 400.
Duration of Exposure: 26 weeks; 4 weeks post exposure recovery period (8 animals/Sex; Control and HD groups only).
Clinical Observations: Daily.
Body Weights: Days -1 and 1; Week 1-4: Twice a week; Week 5-30: Weekly.
Food Consumption: Day 1; Week 1-4: Twice a week; Week 5-30: Weekly.
Ophthalmoscopy: Day -7; Weeks 26 and 30.
Electrocardiography: Week 21 (4 hours post dosing).
Hematology: Weeks -1, 6, 12, 26, and 30.
Clinical Chemistry: Weeks -1, 6, 12, 26, and 30.
Urinalysis: Weeks 6, 12, 26, and 30.
Drug Levels: Not determined.
Vaginal Smear: Day 104 to Day 129.
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortalities: Eight animals (Vehicle Control: 3 ♀; MD: 1♂, 2♀; HD: 1♂, 2♀) died due to technical error during gavage procedure or due to the ether narcosis. Information on ether narcosis was not provided in the method section. The sponsor should be asked to explain deaths due to ether narcosis. Some animals died spontaneously (MD: 2♂; HD: 2♂, 1♀). In the absence of line listing of histopathology data and information on cause of deaths, spontaneous deaths should be treated as drug-related.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Increase in body weights in HD group animals was 12-13% less than that in Control group animals.

Food Consumption: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Electrocardiography: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: Treatment resulted in statistically significantly: increased levels of ALT (σ : MD and HD: 25%; ♀ : MD 19%, HD 50%), AST (σ : MD and HD: 21%; ♀ : HD 33%), and AP (σ : HD 24%; ♀ : HD 24%) and decreased levels of cholesterol (σ : HD 23%; ♀ : HD 15%) and slightly decreased K^+ (7%) in HD females.

Urinalysis: Treatment resulted in statistically significant decrease in the levels of urine potassium in HD females (20%).

Vaginal Smears: Treatment resulted in decreased number of estrous events/animal (MD 15%, HD 29%) in females; data for HD group were statistically significant.

Organ Weights: Treatment resulted in decreased absolute weights of liver (σ : HD 16%; ♀ : HD 14%), spleen (σ : HD 22%; ♀ : MD 14%, HD 27%), adrenals (σ : HD 17%; ♀ : MD 21%, HD 25%), and thymus (σ : HD 29%; ♀ : MD 25%, HD 50%).

Gross- and Histo-Pathology: The sponsor provided a short summary of gross and histopathologic findings. The sponsor should be asked to provide appendices ID 1 to ID 456 and H 1 to H 306 to permit full evaluation of drug-induced gross and histopathologic changes. The following information is taken from the sponsor's summary:

Histopathologic Findings

Organ	Finding	Incidence
Adrenals	Cortical zona glomerulosa atrophy	Increased incidence at HD; completely reversed in females after 4-wk recovery period.
Thymus	Thymic atrophy (moderate)	Increased incidence in HD females; reversed after 4-wk recovery period.
Mammary Gland	Acinar development	MD and HD females had increased incidence; non-reversible.
Cartilage	Suppression of epiphyseal cartilage growth	Increased incidence at HD; non-reversible.

NOAEL: In the absence of histopathologic data, the *NOAEL* could not be determined. Lethal dose was 360 µg/kg/day. The sponsor should be asked to provide additional data.

APPEARS THIS WAY ON ORIGINAL

Rat: 4-wk Subcutaneous Toxicity
Byk Gulden Study 112E/94, 27 June, 1994, Vol. C2.12

b(4)

Study Dates: February, 1988 to July, 1988
Testing Lab: _____
Test Article: Drug suspension in carboxy-methyl-cellulose (2.8 g), Tween 80 (0.16 g), sodium chloride (3.0 g), and distilled water (400 mL).
GLP: Signed GLP Statement was included.

METHODS

Species/Strain: Rat (Wistar).
Animals: 40/Sex; 10/Sex/group.
Route: Subcutaneous.
Dosage: 0 (Vehicle Control); 5 µg/kg/day (LD); 20 µg/kg/day (MD); 80 µg/kg/day (HD). Dosing Volume: 2.5 mL/kg.
Duration of Exposure: 4 Weeks (no recovery period).
Clinical Observations: Daily.
Body Weights: Before the start of treatment and thereafter at weekly intervals.
Hematology: Before the start of treatment and at the end of study.
Clinical Chemistry: Before the start of treatment and at the end of study.
Urinalysis: Before the start of treatment and at the end of study.
Drug Levels: Not determined.
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortalities: There were no mortalities.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in decreased bodyweight gains (♂: HD 14%; ♀: LD 13%, MD 12%, HD 17%).

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: Treatment resulted in statistically significantly decreased alkaline phosphatase (AP) levels in MD and HD males (14% and 29%) and LD females (30%); decrease in the levels of AP was not significant in LD and MD females (18%, each). Levels of total protein were statistically significantly increased (♂: HD 20%; ♀: HD 26%).

Urinalysis: Treatment resulted in increased incidence of ketone bodies in MD and HD males (Vehicle Control 2/10, LD 2/10, MD 3/10, HD 5/10).

Organ Weights: Absolute weights of thymus were decreased (σ : HD 16%; $\text{HD } 22\%$; $\text{HD } 22\%$). Decrease in body weight gain was not high enough to make it necessary to determine relative weights of thymus.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: The incidence of spongiosis of brain in HD animals (5/20) was drug-related

Histopathologic Finding

Organ	Finding	Incidence
Brain	Spongiosis (intercellular edema of spongy layer) in subcortical white matter	σ : HD 2/10; $\text{HD } 3/10$

NOAEL: Due to incidence of spongiosis of brain not seen in 26-week rat (s.c.) study, the HD (80 $\mu\text{g}/\text{kg}/\text{day}$) is the NOAEL.

Rat: 26-wk Subcutaneous Toxicity
Byk Gulden Study 113E/94, 27 June, 1994, Vol. C2.13

Study Dates: February, 1988 to July, 1988 **b(4)**
Testing Lab: _____
Test Article: Drug suspension in carboxy-methyl-cellulose (2.8 g), Tween 80 (0.16 g), sodium chloride (3.0 g), and distilled water (400 mL).
GLP: Signed GLP Statement was included.

METHODS

Species/Strain: Rat (Wistar).
Animals: 40/Sex; 10/Sex/group.
Route: Subcutaneous.
Dosage: 0 (Vehicle Control); 5 µg/kg/day (LD); 20 µg/kg/day (MD); 80 µg/kg/day (HD). Dosing Volume: 2.5 mL/kg.
Duration of Exposure: 26 Weeks (no recovery period).
Clinical Observations: Daily.
Body Weights: Before the start of treatment and thereafter at weekly intervals.
Hematology: Before the start of treatment and at the end of study.
Clinical Chemistry: Before the start of treatment and at the end of study.
Urinalysis: Before the start of treatment and at the end of study.
Drug Levels: Not determined.
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortalities: There were no mortalities.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in body weight loss (♂: HD 23%; ♀: HD 14%).

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: Treatment resulted in decreased levels of cortisol (♂: MD 23%, HD 28%; ♀: MD: 34%, HD 34%).

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: There was an increase in the absolute weights of brain (♂: HD 18%; ♀: HD 9%) and a decrease in the absolute weights of thymus (♂: HD 22%; ♀: HD

15%) and adrenals (σ : HD 16%; ♀ : HD 16%). There was no significant change in relative organ weights.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Incidence of cutaneous abscesses was high in HD animals:

Histopathologic Finding		
Organ	Finding	Incidence
Skin	Cutaneous abscesses (injection site)	σ : LD 1/10, MD 0/10, HD 8/10 ♀ : LD 4/10, MD 2/10, HD 8/10

NOAEL: Due to body weight loss, cutaneous abscesses at the injection site, and decreased thymus weight at HD, the MD (20 $\mu\text{g}/\text{kg}/\text{day}$) is the NOAEL.

APPEARS THIS WAY ON ORIGINAL

Dog: 4-wk Oral Toxicity
Byk Gulden Study 75/94, 13 September, 1994, Vol. C2.7

Study Dates: 14 March, 1994 to 09 May, 1994.
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: 0.5 mL/kg suspension of the drug in PEG 400 enclosed in gelatin capsules
(LD 0.002%, MD 0.008%, HD 0.08%).
GLP: Signed GLP Statement was included.

METHODS

Species/Strain: Dogs (Beagle).
Animals: 14/Sex; 3/Sex/group (Control, LD, MD); 5/Sex/group (HD). In the HD group, 2 animals/sex were used for a 4 week recovery segment of the study.
Route: Oral.
Dosage: 0 (PEG 400 Control); 10 µg/kg/day (LD); 40 µg/kg/day (MD); 400 µg/kg/day (HD).
Duration of Exposure: 4 weeks.
Clinical Observations: Daily.
Body Weights: Days -18 and -4 and two-times/week during exposure period.
Food Consumption: Daily.
Ophthalmoscopy: Weeks -2, -1, 1, 4, and 7 (recovery group): 24 hours post dosing.
Electrocardiography: Weeks -2, -1, 1, 4, and 7 (recovery group): 24 hours post dosing.
Hematology: Weeks -2 and -1 and days 3 and 25 during dosing; Week 8 for recovery group.
Clinical Chemistry: Weeks -2 and -1 and days 3 and 25 during dosing; Week 8 for recovery group.
Urinalysis: Weeks -1, 4, and 7 (recovery group).
Drug Levels: Days 1 and 26 after 0.25, 0.5, 1.0, 1.5, 2.0, 4.0 hours of dosing.
Cortisol Levels: Days -17, -4, 2, and 24. Cortisol levels were not determined using procedures under GLP compliance.
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortalities: There were no mortalities.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in bodyweight loss (♂: MD 1%, HD 4%; ♀: MD 3%, HD 4%).

Food Consumption: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Electrocardiography: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: No toxicologically significant treatment-related effects.

Drug Levels: Not determined.

Cortisol Levels: Treatment resulted in a decrease in the levels of cortisol in HD animals (σ : MD 21%, HD 74%; ♀ : MD 31%, HD 39%).

Organ Weights: Relative weights of adrenals were decreased (σ : HD 25%; ♀ : HD 33%).

Gross Pathology: No toxicologically significant treatment-related effects.

APPEARS THIS WAY ON ORIGINAL

Histopathology:

Histopathologic Findings

Organ	Finding	Incidence
Adrenals	Atrophy of the cortex	♂: HD 3/3, Recovery 2/2; ♀: HD 2/3
Thymus	Involuted thymus	♂: C 3/3, LD 3/3, MD 2/3, HD 3/3, Recovery 2/2; ♀: C 3/3, LD 3/3, MD 3/3, HD 3/3
	Presence of cyst	♀:LD 1/3, HD 2/3
Lymph Node	Lymphocytic depletion of cortex	♂: C 1/3, HD 3/3; ♀: HD 2/3
Kidney	Red brown pigmented granules in tubular epithelium	♂: HD 2/3, Recovery 2/2; ♀: MD, HD: 1/3; Recovery: 1/2
Liver	Centrilobular hepatocellular hypertrophy	♂: LD 2/3, MD 3/3, HD 3/3, Recovery 2/2 ♀: LD 2/3, MD 1/3, HD 2/3, Recovery 1/2
Lung	Lymphocytic interstitial infiltration and inflammatory reaction	♂: C 1/3, LD 1/3, MD 3/3, HD 3/3, Recovery 2/2; ♀: C 1/3, LD 3/3, MD 2/3, HD 2/3, Recovery 1/2

NOAEL: Because of body weight loss and decreased cortisol levels and histopathologic lesions (adrenals, thymus, lymph node, kidney, and liver) at HD, the MD (40 µg/kg/day) is the NOAEL.

Dog: 2-wk Intravenous Toxicity
Byk Gulden Study 154/94, 06 April, 1995, Vol. C2.5

Study Dates: 13 June, 1994 to 4 July, 1994
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: 0.004% solution of Ciclesonide in 10 g ethanol, 1, 2-propylene glycol, and 100 mL of H₂O.
GLP: Signed GLP statement was included.

METHODS

Species/Strain: Dog (Beagle).
Animals: 10/Sex; 2/Sex/group.
Route: Intravenous.
Dosage: 0 (Saline Control); 0 (Vehicle Control); 20 µg/kg/day (LD); 40 µg/kg/day (MD); 80 µg/kg/day (HD). Dosing volumes for saline control, vehicle control, LD, MD, and HD were 2.0, 2.0, 0.5, 1.0, and 2.0 mL/kg, respectively.
Duration of Exposure: 14 days; duration of infusion: 20 minutes.
Clinical Observations: Daily.
Body Weights: Days -18, -4, 1, 4, 8, 11, and 15.
Food Consumption: Daily.
Ophthalmoscopy: Week -2 (saline control, LD, MD, HD), Week -1 (vehicle control), and Week 2.
Hematology and Hemolytic Observations: Days -13, -6, 3, and 11 for hematology and days 1 and 12 for hemolytic observations.
Clinical Chemistry: Days -13, -6, 3, and 11.
Urinalysis: Days -7, 4, and 8.
Drug Levels: 0, 0.33, 1.0, 2.0, 3.0, and 6 hours post dosing on Days 1 and 12.
Organ Weights, Gross- and Histopathology: At termination.

RESULTS

Mortalities: There were no mortalities.
Clinical Signs: No toxicologically significant treatment-related effects.
Body Weights: No toxicologically significant treatment-related effects.
Food Consumption: No toxicologically significant treatment-related effects.
Ophthalmoscopy: No toxicologically significant treatment-related effects.

Hematology and Hemolytic Observations: Reduced erythrocyte counts (18%) and hemoglobin concentration (17%) in HD animals was not biologically significant. Treatment resulted in hemolysis (MD, HD, Vehicle Control: Severe; LD: Moderate) immediately at the end of infusion and lasted for 6 hours or longer (actual duration not indicated). The hemolysis was detected by visual inspection of serum samples after centrifugation.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: Incidence of hematuria (MD 3/4; HD 4/4) was reported. Urinalysis conducted 24 hours post dosing did not show increased hemoglobin concentrations.

Drug Levels: Not determined.

Organ Weights: No toxicologically significant treatment-related effects.

Gross Pathology: In one HD male, thymus almost completely vanished. There were no other toxicologically significant treatment-related effects.

Histopathology:

Histopathologic Findings

Organ	Finding	Incidence
Adrenals	Zona glomerulosa vacuolation	MD 1/4; HD 2/4
Thymus	Involuted thymus (thymic atrophy)	All animals of all groups but more severe in MD & HD
Lymph Nodes	Lymphocytic depletion in the secondary follicles of cortex	HD 3/4
Bone Marrow	Occurrence of fat vacuoles	Vehicle Control 2/4; LD 3/4; MD 3/4; HD 2/4
Liver	Deposits of Lipofuscin pigments	Saline Control 1/4; Vehicle Control 1/4; LD 2/4; MD 4/4; HD 4/4.
Injection Sites	Local Irritant Effect (Thrombophlebitis)	MD 1/4; HD 3/4

NOAEL: Due to incidence of severe thymic atrophy and adrenal vacuolation at MD and HD, the LD (20 µg/kg/day) is the NOAEL.

SUMMARY OF TOXICOLOGY

In a 13-wk oral toxicity study in mice, treatment with Ciclesonide (50, 150-900, and 450 $\mu\text{g}/\text{kg}/\text{day}$) resulted in dose dependent decrease in bodyweight gains in females and incidence of follicular atrophy of spleen in the 150-900 $\mu\text{g}/\text{kg}/\text{day}$ group in both sexes. Signed GLP statement and data on clinical chemistry and urinalysis were not provided. Therefore, NOAEL could not be determined and the target organs of toxicity could not be identified.

In a 4-wk oral toxicity study in rats, treatment (100, 450, and 2000 $\mu\text{g}/\text{kg}/\text{day}$) resulted in decreased body weight gains at HD in males and at MD in females, increased (statistically and biologically significant) levels of ALT (MD, HD) in females and decreased (statistically and biologically significant) levels of urine potassium (HD). There was drug-induced reduction in the number of estrus events/animal (HD) in females. In addition, treatment resulted in increased relative weights of brain (HD males) and decreased relative weights of adrenals (HD) and thymus (MD, HD). Histopathological changes were: atrophy of adrenal cortex (HD) and thymus (HD); depletion of lymphocytes in the cortex of mesenteric lymph nodes (HD females); alveolarization of mammary gland (HD); atrophy of skin (HD); bone marrow cell depletion (HD), disorganized epiphysis (HD), megakaryocytic degeneration (HD), and hyperostosis (HD) of tibia. The NOAEL was 450 $\mu\text{g}/\text{kg}/\text{day}$. The target organs of toxicity were adrenals, thymus, mesenteric lymph nodes, mammary gland, skin, and bone.

When the drug (80, 360, 1600 $\mu\text{g}/\text{kg}/\text{day}$) was administered to rats orally for 26 weeks, treatment resulted in 5 mortalities (2 MD, 3HD) and decreased body weights (HD). Levels of ALT (HD females) and alkaline phosphatase (HD) were increased and levels of cholesterol (HD) and urine potassium (HD) were decreased. There was drug-related decrease in the number of estrus events/animal (MD, HD females). Absolute weights of liver (HD), spleen (HD), adrenals (HD females), and thymus (HD males, MD, HD females) were decreased. Drug-related histopathological changes were: increased incidence of zona glomerulosa (HD), thymic atrophy (HD females), acinar development in mammary glands (MD and HD females), and suppression of epiphyseal cartilage growth (HD). In the absence of histopathologic data, the NOAEL could not be determined and target organs of toxicity could not be fully identified. Lethal dose was 360 $\mu\text{g}/\text{kg}/\text{day}$. The sponsor should be asked to provide appendices ID 1 to ID 456 and H 1 to H 306 and explain deaths due to ether narcosis and spontaneous deaths during this study.

In a 4-week toxicity study (subcutaneous route) in rats, treatment (5, 20, and 80 $\mu\text{g}/\text{kg}/\text{day}$) resulted in decreased bodyweight gains (HD males, LD females). Levels of

total protein increased (HD). Incidence of occurrence of ketone bodies (in urine samples) increased at MD (males) while the absolute weight of thymus decreased (HD). The only histopathologic finding was incidence of spongiosis in subcortical white matter of brain (HD). The NOAEL was 80 µg/kg/day and the target organs of toxicity was thymus [spongiosis of brain was not seen in the 26 week rat (s.c.) study]. When the same dosage of the drug were administered via same route (s.c.) for 26 weeks, treatment resulted in body weight loss (HD) and decreased levels of cortisol (MD, HD). The only histopathologic finding was the incidence of cutaneous abscesses at the injection sites (80 µg/kg/day). The NOAEL was 20 µg/kg/day and the target organs of toxicity were adrenals, thymus, and skin. Signed GLP statements were not provided for either study.

In a 4-week oral toxicity study in dogs, treatment (10, 40, and 400 µg/kg/day) resulted in body weight loss at MD, decreased levels of cortisol at MD, and decreased absolute weights of adrenals at MD (males) or LD (females). Histopathological changes were atrophy of adrenal cortex (HD), lymphocytic depletion of cortex in lymph nodes (HD), centrilobular hepatocellular hypertrophy in liver (LD), and increased incidence of lymphocytic interstitial infiltration and inflammatory reaction in lungs (MD males and LD females). The NOAEL was 40 µg/kg/day and the target organs of toxicity were adrenals, thymus, lymph nodes, liver, and lung.

When the drug was administered to dogs for 2 weeks via intravenous route, treatment (20, 40, and 80 µg/kg/day) resulted in the incidence of hematuria (MD) and hemolysis (Moderate: LD; Severe: MD, HD, Vehicle Control). Histopathological findings consisted of zona glomerulosa vacuolation in adrenals (MD, HD), lymphocytic depletion in the secondary follicles of lymph node cortex (HD), incidence of fat vacuoles in the bone marrow (vehicle control and all treatment groups), increased incidence of deposits of lipofuscin pigments in the liver (LD, MD, HD), and thrombophlebitis at the injection sites (MD, HD). Atrophy of thymus was seen in all groups but it was more severe in MD and HD groups. The NOAEL was 20 µg/kg/day and the target organs of toxicity were adrenals, thymus, lymph nodes, bone marrow, and liver.

SPECIAL TOXICITY

Dog: Hemolytic potential following intravenous administration
Byk Gulden Study 33/95, 24 April, 1995, Vol. C2.13

Study Dates: 03 November, 1994 to 13 April, 1995
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: 0.005% Ciclesonide containing 10 g ethanol and 40 g of 1, 2 polypropylene glycol in 100 mL of distilled water.
GLP: The study was conducted under GLP compliance of European Community.

Test article was administered to dogs (2/Sex/group) via i.v. at 0.004 mg/kg/day (dosing volume: 0.08 mL/kg), 0.008 mg/kg/day (dosing volume: 0.16 mL/kg), and 0.02 mg/kg/day (dosing volume: 0.4 mL/kg) for 3 days. The concentration of the drug (50 µg/mL) in this study was about 25-fold of the concentration in the *in vitro* study (2.1 µg/mL; see page 27). Control article (vehicle) was administered to 2 dogs/Sex for 3 days (dosing volume: 0.4 mL/kg) and was repeated at lower volume (0.02 and 0.04 mL/kg) after a wash out period of one month. Time of sampling were 0, 1, 2, 4, and 6 hours post dosing on Day 3 for test groups and 0, 1, 2, 4, and 6 hours post dosing on Days 3 and 39 for vehicle control group. Treatment with Vehicle (0.4 mL/kg) and HD resulted in hemolysis (detected by visual inspection of serum samples after centrifugation); hemolysis in these two groups persisted up to 2 hours and decreased gradually to a mild hemolysis after 6 hours. Three out of 4 LD animals showed mild hemolysis after 1 hour and all MD animals showed a moderate hemolysis at 1 hour post dose decreasing to mild hemolysis after 2 hours. Animals treated once with smaller volume of the vehicle (0.02 and 0.04 mL/kg) showed no visually detectable hemolysis; however, plasma oxihemoglobin determinations carried out on these animals showed a two-fold increase (over saline controls) in animals treated with 0.04 mL/kg and no effect on animals treated with 0.02 mL/kg of vehicle. Serum cortisol levels were suppressed at day 3 in 3/4 MD and 4/4 HD animals. These data suggest that extent of hemolysis depended on the dosing volume. Levels of oxihemoglobin did not change in 0.02 mL/kg vehicle treated animals.

Guinea Pig: Irritation Potential following epicutaenous administration
Byk Gulden Study 123/94, 19 August, 1994, Vol. C2.13.

Study Dates: 02 May, 1994 to 19 August, 1994
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: Ciclesonide in 96% ethanol.
GLP: The study was conducted under GLP compliance of European Community.

Female guinea pigs (Control: 2/group; Treatment: 3/group) were treated topically with 0% (vehicle control), 0.1%, 1%, and 10% solutions of the drug (dosing volume: 0.015 mL). On Day 2 and 5, 0.1 mL of 50% FCA (Freund's adjuvant) was injected intracutaneously to each animal (shoulder area). On Day 9, animals were treated topically on one side with control or test compound in shoulder area for 24 hours which was followed by a recovery period of 24 hours. The skin was examined on Day 11 for signs of irritation. Treatment resulted in no signs of irritation.

Rabbit: Local (Intravenous, Paravenous, or Intra-arterial) Tolerance Study
Byk Gulden 72/95, 13 April, 1995, Vol. C2.13.

Study Dates: 22 February, 1995 to 13 April, 1995
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: 0.005% Ciclesonide in 9.6% (w/v) ethanol and 40% (w/v) 1, 2 propylene glycol in distilled water.
GLP: The study was conducted under GLP compliance of European Community.

Rabbits (3 females/group) were administered Test article (dosing volume: i.v.: 1 mL; p.v. and i.a.: 0.5 mL) into one ear and Control article [9.6% (w/v) ethanol and 40% (w/v) 1, 2 propylene glycol in distilled water; same dosing volume as in case of Test article] into the other ear via i.v. (in the marginal ear vein), p.v. (in the marginal ear vein), or i.a. (in the central ear artery). The animals were observed for 8 days to evaluate tissue reaction. On Day 9, the animals were killed and ears processed for histologic examination. In 2/3 cases in which the ears were treated with the drug via i.v., the media cells of the injected vein were mildly vacuolated. In an ear treated with the placebo via i.v., incidence of moderate vasculitis and perivasculitis with Eosinophil cell infiltration (1/3) was observed. In all ears treated with drug or placebo via p.v. or i.a., moderate or severe necrotizing inflammations or a mild to moderate vasculitis and perivasculitis were seen. The inflammation potential of the drug was greater with paravenous and intra-arterial routes than with intravenous route.

***In Vitro* Rat, Dog, and Human blood compatibility (Erythrocyte Stability) Study**
Byk Gulden 8/95, 14 March, 1995, Vol. C2.13.

Study Dates: 05 January, 1995 to 14 March, 1995
Testing Lab: Byk Gulden Institute of Pathology and Toxicology, Germany.
Test Article: 0.005% Ciclesonide in 96% ethanol (5 g), 1,2-propylene glycol (20 g) and distilled water (50 mL).
GLP: The study was conducted under GLP compliance of European Community.

Hemolysis-free blood samples from rats (lateral tail vein), dogs (jugular vein), and humans (arm vein) were mixed with test article (2.1 µg/mL) or placebo (solution containing all the constituents of the formulation except the drug) did not result in hemolysis or erythrocyte clumping. Based on macroscopic and photometric determinations, the sequence of erythrocyte stability was human>dog>rat. Thus, treatment with drug or placebo does not have hemolytic potential.

SUMMARY OF SPECIAL TOXICITY

At a concentration of 50 µg/mL used in the i.v. study in dog, treatment with the drug resulted in hemolysis at all doses as well as in the vehicle control (ethanol and polypropylene glycol) group; there was a dose dependent increase in the degree of hemolysis from vehicle control to HD group. The hemolytic potential of the drug depended on the dosing volume indicating such preparation will induce hemolysis. An *in vitro* rat, rabbit, and dog blood compatibility test resulted in no hemolysis (concentration of the drug: 2.1 µg/mL) and the order of erythrocyte stability was as follows: humans>dogs>rats. Epicutaneous administration of the drug (Concentration: 1-100 mg/mL) in guinea pigs resulted in no signs of irritation. Results from local (intravenous, paravenous, or intra-arterial) tolerance study in rabbits (Concentration of the drug: 50 µg/mL) showed histologic findings for paravenous and intraarterial tests being more severe than findings in an i.v. test. In paravenous and intraarterial tests, placebo caused higher grade of severe necrotizing inflammation than the drug product.

OVERALL SUMMARY AND EVALUATION

Toxicology: In preclinical toxicity studies via oral, subcutaneous, and intravenous routes, Ciclesonide exhibited toxicity profile that is typical of glucocorticoid steroids. In a 13-wk oral study in mice, NOAEL could not be determined and target organs of toxicity could not be identified due to lack of clinical chemistry and urinalysis data. The sponsor should be asked to provide these data as well as a statement as to whether this study was conducted under the compliance of GLP.

In rats, a 4-wk oral treatment with the drug resulted in a NOAEL of 450 µg/kg/day and the target organs of toxicity were adrenals, thymus, mesenteric lymph nodes, mammary gland, skin, and bone. When the drug was administered for 26 weeks, the NOAEL and target organs of toxicity could not be established due to lack of line listing of histopathology data. Lethal dose was 360 µg/kg/day. In both 4- and 26-week oral rat studies, there was drug-induced reduction in the number of estrus events/animal at doses of 2000 and 360 µg/kg/day, respectively. The sponsor should be asked to include this information in the informed consent section of the clinical protocol. The sponsor should also be asked to provide appendices ID 1 to ID 456 and H 1 to H 306 to allow complete review of this study. In addition, the sponsor should explain deaths due to ether narcosis.

In rats, a subcutaneous administration of the drug for 4 weeks resulted in a NOAEL of 80 µg/kg/day and thymus was the target organ of toxicity. When the drug was administered via same route (s.c.) for 26 weeks, the NOAEL was 20 µg/kg/day and the target organs of toxicity were adrenals and skin. Signed GLP statements were not provided for either study.

In dogs, a 4-week oral administration of the drug resulted in NOAEL of 40 µg/kg/day and the target organs of toxicity were adrenals, thymus, lymph nodes, liver, and lung.

In dogs, when the drug was administered intravenously for 2 weeks, the NOAEL was 20 µg/kg/day and the target organs of toxicity were adrenals, thymus, lymph nodes, bone marrow, and liver.

These studies did not reveal any additional toxicity that was not revealed by studies conducted via inhalation route.

Special Toxicity: In dogs, intravenous administration of the drug in ethanol and polypropylene glycol vehicle (50 µg/mL) caused hemolysis. In guinea pigs, an epicutaneous administration of the drug resulted in no signs of irritation. In rabbits, administration of the drug via i.v. route was better tolerated locally than administration via paravenous or intra-arterial routes. In *in vitro* rat, rabbit, and dog blood compatibility tests, there were no incidences of hemolysis perhaps due to 25 times lower concentration of the drug used (2 µg/mL). The order of stability of erythrocytes was: humans>dogs>rats.

RECOMMENDATION

The sponsor should be asked to provide data on clinical chemistry and urinalysis for the 13-week oral mouse study (No. 185/95); appendices ID 1 to ID 456 and H 1 to H 306 and explanation for mortalities due to ether narcosis in the 26-week oral rat study (No. 223/95). In 4- and 26-week oral rat studies, there was drug-induced reduction in the number of estrus events/animal at doses of 2000 and 360 µg/kg/day, respectively. This information should be included in the informed consent section of the clinical protocol. The sponsor should also provide Statement of GLP Compliance for 13-week oral mouse study (No. 185/95) and 4- and 26-week rat studies via subcutaneous route (Study No. 112E/94 and 113E/94).

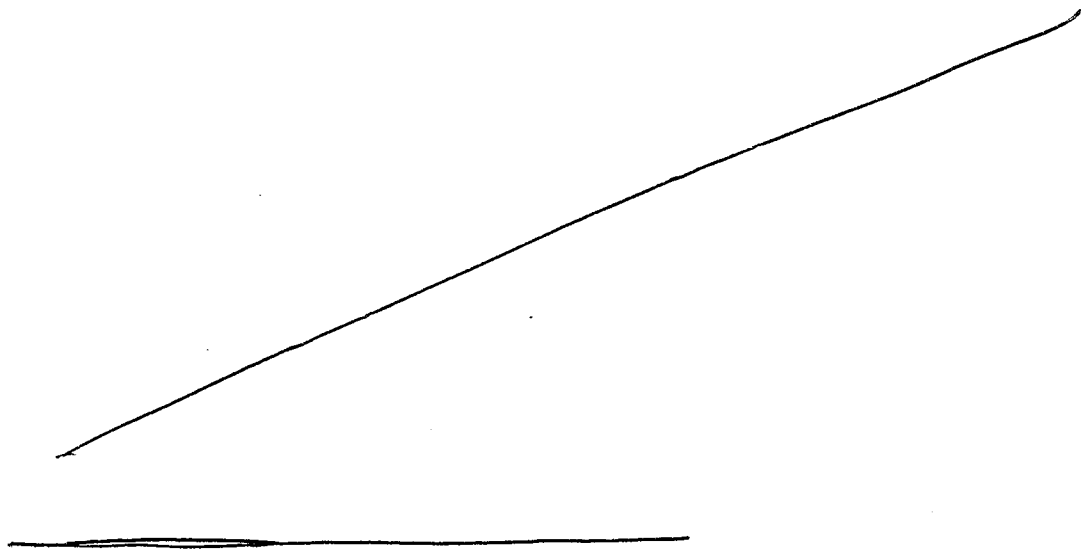
Points discussed with Medical Officer:

In 4- and 26-week oral rat studies, there was drug-induced reduction in the number of estrus events/animal at doses of 2000 and 360 µg/kg/day, respectively. The medical officer suggested that this information should be included in the informed consent section of the clinical protocol.

Information for Investigator's Brochure/Informed Consent:

In rats, Ciclesonide induced prolongation of estrus events at a dose ≥ 360 µg/kg/day.

Draft Letter to the Sponsor:



b(5)

Satish C. Tripathi, Ph.D.
Pharmacology/Toxicology Reviewer

Original IND
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ATTACHMENT 3.