

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-433

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult
Amendment

NDA number: 21-433

Date/type of submission: 11/13/03

Date of Amendment: 4/16/04

Add the following to the Consult Review of 4/14/04 under the Description of the Consult heading.

There is no consideration of the 120-dose inhaler 44 ug/actuation as a worse case scenario since to achieve the maximum recommended daily inhalation dose of 1760 ug would require 20 actuations twice daily. This dosing regimen is considered unrealistic and impractical.

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____

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/s/

Lawrence Sancilio
4/16/04 03:49:52 PM
PHARMACOLOGIST

Joseph Sun
4/19/04 03:16:33 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult

NDA number: 21-433
Date/type of submission: 11/13/03
Request date: 2/17/04, 2/18/04
Sponsor: GlaxoSmithKline Inc.

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: Division of Pulmonary and Allergy Drug Products
HFD: 570
Review completion date: 4/16/04

Drug: Fluticasone propionate HFA aerosol; _____
120 actuations/can; 44, 110 and 220 ug/actuation.

Drug class: Glucocorticoid

Indication: Treatment of asthma.

Route of administration: Inhalation

Response to Chemistry Consult Requested by Alan Schroeder, Ph.D.

Description of the Consult

This is a request to determine if the proposed acceptance criterion for the daily exposure _____ and the proposed acceptance criterion of the _____ in the fluticasone propionate HFA aerosol products are acceptable. The worst case scenario for the maximum exposure for _____ and the _____ is reviewed. This occurs in the 120-dose inhaler, 110 ug/actuation, (there are a total _____ where there are 10 of daily doses based on 8 actuations twice daily to achieve the maximum recommended daily inhalation dose of 1760 ug. There is no consideration of the 120-dose inhaler, 44 ug/actuation, as the worst case scenario since to achieve the maximum recommended daily inhalation dose, the dosing regimen (20 actuations twice daily) is unrealistic and impractical.

Review

_____ possesses a structure alert. No toxicity data is available. The proposed acceptance criterion for this _____ is _____. Based on 16

actuactions/day (— ng/actuation), the total daily human exposure is — ng or — ng/kg/day. The proposed acceptance criterion of — is unacceptable since the maximum daily exposure of — ng/kg is above the safety concerned threshold dose of — ng/kg from the database.

The proposed acceptance criterion for — is — . Based on 16 actuactions/day (— ug/actuation), the total human daily exposure is — ug or — ug/kg. In a 2-year carcinogenicity study, — mg/kg based on a 250 g rat and 15 g of food consumed daily) was administered in the diet. There were no adverse effects, and the NOAEL was — ug. A safe inhalation dose is — ug/kg, (1/1000 of the NOAEL) determined from using an uncertainty safety factor of 1000 due to route and species difference. The proposed acceptance criterion of — is acceptable as the exposure (— ug) is below the safe inhalation dose.

The request addressed the proposed acceptance criterion for daily exposure of — from the 120 actuactions/can products. The daily dose is 16 actuactions a day, and there are 10 daily doses/can. The proposed acceptance criterion for the daily — exposures is presented in the following table.

	Proposed Acceptance Criterion
	Not Greater than
	Not Greater than
	Not Greater than
	Total: Not Greater than

Summary and Overall Evaluation

The proposed acceptance criterion of the _____, which features a structure alert, is unacceptable since the daily exposure will be _____ and above the safety concern threshold of _____ from the database. This occurs when under the worse case scenario, 16 actuations of the 110 ug/actuation are administered to achieve the maximum recommended daily dose of 880 ug twice daily or 1760 ug. However, since this is unrealistic, the most realistic and practical approach to achieve the maximum recommended dose will be the 220 ug/actuation product which will require 8 actuations. Consequently, under this dosing regimen, the daily exposure of _____ will be _____ ng/kg, the safety concern threshold, thereby making the proposed acceptance criterion acceptable. The proposed acceptance criterion of the _____, is acceptable since the daily exposure of _____ ug/kg is below the safe inhalation dose of _____ /kg.

The proposed acceptance criterion of _____ exposure being not more than _____ is acceptable. At this level, the exposure is _____ ug/day which is below the acceptable level of 1000 ug/day determined from the _____

Recommendation

The proposed acceptance criteria for the _____ are acceptable.

Reviewer's signature: _____

Supervisor's signature: Concurrence - _____

Non-Concurrence - _____
(See memo attached)

cc. A Schroeder

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/s/

Lawrence Sancilio
4/16/04 01:13:15 PM
PHARMACOLOGIST

Joseph Sun
4/16/04 01:17:43 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult

NDA number: 21-433
Date/type of submission: 11/13/03
Request date: 2/26/04
Sponsor: GlaxoSmithKline Inc.

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: Division of Pulmonary and Allergy Drug Products
HFD: 570
Review completion date: 4/14/04

Drug: Fluticasone propionate HFA aerosols, 44, 110 and 220 ug/actuation

Drug class: Glucocorticoid

Indication: Treatment of asthma.

Route of administration: Inhalation

Response to Chemistry Consult Requested by Alan Schroeder, Ph.D.

Description of the Consult

This is a request to determine the acceptability of the proposed daily exposures of the _____ in the Fluticasone propionate HFA aerosol products. Under the worst scenario, there are 10 daily doses/can/product (120 actuations _____), maximum daily dose: 16 actuations/day) from which the proposed daily exposures were determined.

Review

The following table lists the _____ with their proposed daily exposures based on 10 daily doses (worst scenario) per can, and the assessment as to whether the exposures were acceptable. Assessment of their acceptability was made from the data supplied by the sponsor or found in the Micromedex Integrated Index database. The following formulas were used in determining the daily human exposure _____

3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

/

Summary and Evaluation

The estimated daily exposures of the _____ at the proposed specifications in the Flovent HFA Inhalation Aerosol inhalers are at acceptable safe levels.

Recommendation

There is no safety concern for the estimated daily exposure of the _____ at the proposed specifications in the Flovent HFA Inhalation Aerosol inhalers.

Reviewer's signature: _____

Supervisor's signature: Concurrence - _____

Non-Concurrence - _____
(See memo attached)

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/s/

Lawrence Sancilio
4/14/04 02:51:51 PM
PHARMACOLOGIST

Joseph Sun
4/14/04 03:52:40 PM
PHARMACOLOGIST
I concur.

10 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-433

Review number: 000

Serial number/date/type of submission: 000/2/26/02/ original

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Glaxo Inc.

5 Moore Drive

Research Triangle Park, NC 27709

Manufacturer for drug substance: Fluticasone propionate: Glaxo Wellcome Operations, Montrose and Ware United Kingdom, Jurong, Singapore, and Everux, France.

Reviewer name: Lawrence F. Sancilio, Ph.D.

Division name: Division of Allergy and Pulmonary Drug Products

HFD: 570

Review completion date: 12/20/02

Drug:

Trade name: Unknown

Generic name: Fluticasone propionate

Code name: CCI18781

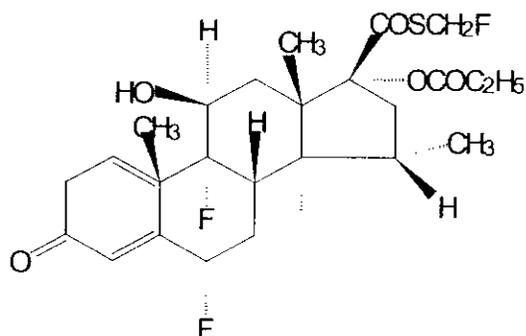
Chemical name: S-fluoromethyl 6, 9 -difluoro-11 -hydroxy-16 - methyl-3-oxo-17-propionyloxyandros ta-1, 4-diene-17 -carbothioate

CAS registry number: 80474-14-2

Mole File Numbers: Unknown.

Molecular Formula/ Molecular Weight: C₂₅H₃₁F₃O₅S, 500.6

Structure:



Relevant INDs/NDAs/DMFs:

IND 53,502,
NDA 20-121 (fluticasone propionate nasal spray), NDA 20-548 (fluticasone propionate as a metered dose inhaler using chlorofluorocarbon propellants), NDA 20-549 (fluticasone propionate

as a Rotadisk dry powder inhaler),

Drug class: Glucocorticoid

Indication: Treatment of asthma.

Clinical formulations:

Component	Theoretical Amount/Actuation Delivered Through the Valve		
	44 µg 120 Actuations	110 µg 60 and 120 Actuations	220 µg 120 Actuations
Fluticasone propionate	50 µg ^a	125 µg ^a	250 µg ^a
HFA134a Hydrofluoroalkane	/		

^a targeted quantity

Route of administration: Inhalation

Proposed use: The maintenance treatment of asthma as prophylactic therapy in adolescent patients 12 years of age and older.

Dose: 440 - 880 mcg twice a day

**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary

- I. Recommendations
 - A. Recommendation on Approvability
Recommend approvability.
 - B. Recommendation for Nonclinical Studies
None.
 - C. Recommendations on Labeling

The following changes (**BOLD**) are recommended in the cited sections.

Pregnancy: Teratogenic Effects: Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively, (less than the maximum recommended daily inhalation dose in adults on a mcg/m²), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. **No teratogenicity was seen in the rat at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m²).**

In the rabbit, fetal weight and cleft palate were observed following subcutaneous doses of 4 mcg/kg :

However,.....

OVERDOSAGE

- II. Summary of Nonclinical Findings
 - A. Brief Overview of Nonclinical Findings

Fluticasone propionate is a potent fluorinated glucocorticoid. Unlike other glucocorticoids, fluticasone propionate increases both sodium and potassium excretion. In mice rats, dogs and humans, fluticasone propionate undergoes high first pass metabolism being hydrolyzed to the non-toxic -COOH metabolite. Excretion of parent compound and its metabolites is primarily fecal.

In acute toxicity studies in mice, rats and dogs, toxic manifestations were characteristic of glucocorticoids. Due to high first pass metabolism, no toxicity was seen by the oral route in rats and mice; this accounted for juvenile rats to be more sensitive by the subcutaneous than the oral route.

In multidose toxicity studies in rats and dogs, fluticasone propionate administered by the inhaled route as a dry powder or by a mixture of two chlorofluorocarbon propellants (CFC), the toxicity seen was characteristic of glucocorticoids. In dogs, there was evidence of inflammation due to local irritation and infection due to the compromised immune system. In a 13-week inhalation study in dogs, a direct comparison was made with fluticasone propionate being administered in the CFC and HFS134 propellants; both formulations showed a similar glucocorticoid toxicity profile except that the glucocorticoid effects of fluticasone propionate were slightly higher with the CFC propellant. Both formulations of fluticasone propionate showed local irritation to the same degree to the respiratory tract.

In juvenile dogs, 4-week and 7-week and 1-year inhalation studies were conducted with the fluticasone propionate-HFA 134a formulation. No toxicity was seen in the 4-week study; in the 7-week study there were the characteristic glucocorticoid effects. In addition, there was a decrease in the width of the tracheal ring in the M. In the one-year study, the severity of the toxic glucocorticoid effects, necessitated that the dose be ultimately lowered after 8 weeks. Decreased tracheal development was also seen in both sexes. However, there was no disorientation of the tracheal rings to be clinically concerned. The respiratory tract also showed pathologic changes in the larynx, carina and lungs indicating local toxicity.

Fluticasone propionate was not genotoxic or mutagenic. In the carcinogenicity studies in rats and mice, fluticasone propionate was not tumorigenic. In reproductive studies when fluticasone propionate was administered by the subcutaneous route, fertility was not affected, but fetotoxicity and teratogenicity was seen in mice, rats and rabbits. No teratogenicity was seen by the inhaled route in rats or by the oral route in rabbits. Very little fluticasone propionate crosses the placenta of rats and rabbits following oral administration. Radioactivity was found in the milk of lactating rats following subcutaneous administration of tritiated fluticasone propionate.

A. Pharmacologic Activity

Fluticasone propionate is a potent glucocorticoid.

B. Nonclinical Safety Issues Relevant to Clinical Use

None.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

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HFD: 570

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY: NA.

II. SAFETY PHARMACOLOGY: NA.

III. PHARMACOKINETICS/TOXICOKINETICS:

Study title: Plasma Levels of fluticasone propionate following inhalation administration to pregnant rats and their progeny in utero, No. GDM/94/113

In the study which evaluated the effect of inhaled fluticasone propionate administered to pregnant AHA rats and their progeny in utero which was reviewed by Shannon Williams (Review of IND 53,502, Submission date: 6/18/97 Review date, 9/12/97), plasma levels were determined by a radioimmunoassay on days 7 and 16 of gestation, prior to and at 10 minutes following administration of the inhaled fluticasone propionate. The limit of quantitation was \sim pg/ml. There were an air control group, a HFA control group and 3 fluticasone propionate treated groups.

Results

The targeted exposures were 0.4 mcg/L for 20 min, 0.45 mcg/L for 1 h and 2 mcg/L for 1 h. The mean achieved chamber concentrations were 0.445 mcg/L for 20 min, 0.686 mcg/L for 1 h and 1.817 mcg/L for 1 h. This corresponded to daily inhalation doses of 5.5, 25.7 and 68.7 mcg/kg.

In the air-control group (Day 7, pre-dose) and in the HFA-control group (day 7, 10 min post dose), 1/4 animals in each group had levels of fluticasone propionate. The sponsor attributed this to contamination. The results in the following table indicate that there was accumulation upon repeated administration especially at the HD.

Group	Mean Concentration, pg/ml			
	Day 7		Day 16	
	Pre-Dose	10 min Post Dose	Pre-Dose	10 min Post Dose
Control, Air	BLQ ^a	BLQ	BLQ	BLQ
Control, HFA	BLQ	BLQ ^b	BLQ	BLQ
LD	BLQ	BLQ	BLQ	297
MD	BLQ	668	BLQ	909
HD	BLQ	1299	BLQ	>2500

^a one animal showed a plasma fluticasone propionate level of \sim pg/ml.

^b one animal showed a plasma fluticasone propionate level of \sim pg/ml.

BLQ, Below the limit of quantitation, \sim pg/ml

Conclusion

In rats, fluticasone propionate systemic absorption and accumulation occurred following inhalation administration from days 6 to 16 of gestation.

IV. GENERAL TOXICOLOGY:

Study title: Preliminary 4-week inhalation tolerance study in juvenile dogs

Key study findings: There was systemic absorption as evidenced by plasma levels.

Study no: WPT/93/510

Volume #, and page #: Not available.

Conducting laboratory and location: —

Date of study initiation: 11/17/98

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot # and % purity: MDI (Batch No. U92/027A)

Formulation/vehicle: /HFA (GR106642X)

Method:

Two juvenile M and 2 F beagle dogs, approximately 10-weeks old and weighing between 4.1 and 5.6 kg was administered fluticasone propionate by inhalation via the oropharyngeal route. Each dog received approximately 30 metered doses (42.8 mcg per dose) administered in divided doses not less than 4 h apart daily for 4 weeks. Clinical signs, body weight, ophthalmoscopy, hematology, clinical chemistry and urinalysis were determined. Blood samples were taken on day 1 and during week 4, before dosing and 2, 10, 20 and 40 min and 2, 4 and 24 h after dosing. At necropsy, bone marrow (myeloid:erythroid ratio) and macroscopic pathology analysis were conducted. There were no control animals to make a comparison.

Results:

From the dosing apparatus 61% of the dose was recovered. Thus, each dog received a total daily dose of 501 µg; this related to 73 and 91 mcg/kg/day for the M and 102 and 104 µg/kg/day for the F. Since there were no control groups, no definitive analysis could be made from the small changes seen. The dogs apparently tolerated the dose of fluticasone propionate as there were no deaths, no clinical signs, no eye changes or changes in body weight, hematology, clinical chemistry, urinalysis, gross macroscopic changes and bone marrow changes. There was evidence of systemic absorption as peak plasma levels occurred between 20 and 40 minutes following administration. However, no definitive conclusion could be made of the pharmacokinetics since prior to administering the fluticasone propionate on the first day, 1 M and 1 F dog showed plasma levels — pg/ml).

Conclusion:

In a pilot 4-week inhalation study, juvenile dogs tolerated daily doses of 83 mcg/kg in M and 102 mcg/kg in F.

Study title: 7-Week pilot inhalation toxicity in juvenile dogs

Key study findings: Atrophy of the adrenal glands; adrenal gland suppression; decreased development of the C20 tracheal ring.

Study no: RD1998/02642/00

Volume #, and page #: Not available.

Conducting laboratory and location: —

Date of study initiation: 11/17/98

GLP compliance: Yes

QA report: yes () no (X)

Drug, lot # and % purity: 988001 and —

Formulation/vehicle: ethanol/HFA

Methods:

Dosing:

Species/strain: Beagle dogs

#/sex/group or time point (main study): Control, 2/sex (shelf); Treated. 3/sex/group

Satellite groups used for toxicokinetics or recovery: None.

Age: 14-19 days.

Weight: 0.61-1.12 kg.

Doses in administered units: 5, 15, 25 mcg/kg

Route, and particle size: Inhalation, head only: —

Observations and times:

Clinical signs: Daily.

Body weights: Daily.

Food consumption: Not recorded.

Ophthalmoscopy: Prior to first dose and at termination.

EKG: Not conducted.

Hematology: Prior to first dose and at termination.

Clinical chemistry: Prior to first dose and at termination.

Urinalysis: Week 3 and day 45.

Girth (abdominal) and Long Bone (5 cm behind the forelegs) measurements: Prior to first dose, week 3 and at termination.

Developmental landmarks (days observed): Eyes and ears opening, tooth eruption and withdrawal from the pack.

Adrenal function test: Weeks 2 and 7 received 1 ml i.v. of ACTH; Blood was withdraw before and 1.5 h after administration.

Toxicokinetics: Blood was collected predose and 5 min and 30 min and 1, 2, 6 and 24 h post dosing on day 1 and during the final week.

Gross pathology: Gross necropsy was conducted on all animals including tracheal measurements.

Organs weighed: See Histology inventory below

Histopathology: See Histology inventory below.

Results:

Mortality: None.

Clinical signs: None.

Body weight Gained: M, LD, +2.6 kg; MD, +2.65kg; HD, +1.84 kg.

F, LD, +1.40 kg; MD, +1.915kg; HD, +1.60 kg.

Food consumption: Not recorded.

Ophthalmoscopy: No effect.

Electrocardiography: Not conducted.

Hematology: No effect.

Clinical chemistry: No effect.

Urinalysis: No effect.

Girth (abdominal) and Long Bone (5 cm behind the forelegs) measurements: No effect.

Developmental landmarks: No effect.

Adrenal function test: HD, the response to ACTH was less than the LD response on days 10 (M, 40%; F, -53%) and 45 (M, -39%; F, -51%).

Toxicokinetics: Note: Plasma levels of fluticasone propionate on day 0 were present prior to dosing with fluticasone propionate. The sponsor indicated that the fluticasone propionate was present in the predose samples from dosed animals and in samples from shelf control animals. No further explanation was offered. The reliability of the results cannot be determined, and consequently the data was not included in the report.

Gross pathology:

Tracheal Measurements: HD, M, Width of the 20th tracheal ring was 20% less than the width of the LD tracheal ring.

Adrenals: Small, M, LD, 0/3; MD, 1/3; HD, 2/3.

F, LD, 0/3; MD, 2/3; HD, 3/3.

Organ weights: Adrenal: Absolute(compared with the LD): HD, M, -40%;

Relative (brain) Absolute(compared with the LD): HD, M,-40%

Histopathology:

Organ/Lesion	Incidence							
	C ^a	LD	M	HD	C ^a	LD	F	HD
Adrenal Diffuse Atrophy Zona fasciculata	0/2	0/3	2/3	3/3	0/2	0/3	2/3	3/3

^a Shelf Control animals

Conclusion

In a 7-week pilot inhalation study in juvenile dogs, doses of 5, 15 and 25 mcg/kg were tested. Changes characteristic of glucocorticoid activity were seen at the MD and HD with M showing greater sensitivity than the F. The M also showed decreased body weight gained and decreased development of the 20th tracheal ring. The NOAEL was 5 mcg/kg and the target organs were the adrenal gland and the 20th tracheal ring.

The following report was not reviewed as it was previously reviewed.

A 52-week inhalation toxicology study in juvenile dogs, No. WPT/95/096, (See review of L. Sancilio, Ph.D., NDA 20-770: Submission date: 9/26/96; Review date, 6/2/97).

Toxicology Summary of Studies in Juvenile Dogs

Preliminary 4-week and 7-week pilot inhalation toxicity studies were conducted in juvenile dogs. In the 4-week trial, the average inhalation doses were 81 mcg/kg for the M and 103 mcg/kg for the F. These dogs were 10-weeks old. There were no control groups in this study. The juvenile dogs tolerated these doses well, as there was no apparent evidence of ophthalmic or macroscopic pathology or changes in body weight, hematology, clinical chemistry, urine and bone marrow. There was some indication of systemic absorption of fluticasone propionate due to the presence of plasma levels. In the 7-week pilot study, the inhalation doses were 5, 15 and 25 mcg/kg. These dogs were 14-19 days old, and the control animals were shelf animals from which some of the comparisons were made. Changes noted at the MD and HD were characteristic of a glucocorticoid, i.e., adrenal atrophy and suppression of the adrenal response to ACTH. However, in the HD, M, there was also a decreased in the development (width) of the 20th tracheal ring. The NOAEL was 5 mcg/kg. In a one-year single inhalation dose study in 10-week old juvenile dogs, the initial dose (126-140 µg/kg) was toxic as a result of severe glucocorticoid effects requiring the dose to be lowered after week 8 to 25 µg/kg. The effect on tracheal ring development was confirmed, as there was a decrease in the size of several tracheal rings in both sexes. However, there was no disorientation of the tracheal rings to be clinically concerned. There were signs of local toxicity as evidence by pathologic changes in the larynx, carina and lungs.

The following submitted Toxicology reports were not reviewed as they were previously reviewed.

A three-month inhalation toxicity study in the CRW rat, No. WPT/94/028; Toxicokinetics, No. GDM/94/024, (See review of Shannon Williams, Ph.D., IND 53,502: Submission date: 6/18/97; Review date, 9/12/97).

A three-month inhalation toxicity study in the dog, No. WPT/92/425028; Toxicokinetics, No. GDM/92/071, (See review of Shannon Williams, Ph.D., IND 53,502: Submission date: 6/18/97; Review date, 9/12/97).

A three-month inhalation toxicity study in the dog, No. WD1998/00282/00;
Toxicokinetics, No. GDM/92/071, (See reviews by W. Mark Vogel, Ph.D., IND 53,502:
Submission dates: 8/18/97 and 8/21/98; Review dates: 8/5/98 and 11/16/98).

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Histopathology Inventory for NDA # 21-433

Study	RD1998/0642/00			
Species	Juvenile Dog			
Adrenals	X ^{ab}			
Aorta	X			
Bone Marrow smear	X ^b			
Femoral head and shaft	X ^b			
Brain	X ^a			
Cecum	X			
Cervix				
Colon	X			
Duodenum	X			
Epididymis	X ^a			
Esophagus				
Eye	X			
Fallopian tube				
Gall bladder				
Gross lesions	X ^b			
Harderian gland				
Heart	X ^a			
Ileum	X			
Injection site				
Jejunum	X			
Kidneys	X ^a			
Lachrymal gland	X			
Larynx with oropharynx and tonsils	X			
Liver and gall bladder	X ^{ab}			
Lungs	X ^{ab}			
Lymph nodes, Cervical	X			
Lymph nodes tracheobronchial	X ^b			
Lymph nodes, mesenteric	X			
Mammary Gland				
Head/nasal cavity				
Optic nerves	X			
Ovaries	X ^a			
Pancreas	X			
Parathyroid	X ^a			
Peripheral nerve				
Pharynx				
Pituitary	X ^a			
Prostate	X ^a			
Rectum	X			
Salivary gland	X			
Sciatic nerve	X			

Seminal vesicles				
Skeletal muscle	X			
Skin	X			
Spinal column	X			
Spleen	X ^{ab}			
Sternum and Bone marrow	X			
Stomach	X			
Testes	X ^a			
Thymus	X ^{ab}			
Thyroid	X ^a			
Tongue	X			
Trachea and Bifurcation	X ^b			
Urinary bladder	X			
Uterus	X			
Vagina	X			
Nictitating Membrane	X			
Nasal chambers	X ^b			
Bronchi	X ^b			
Carina	X ^b			
Soft palate	X ^b			

^b histopathology performed

^a organ weight obtained

X, tissue collected and processed

V. GENETIC TOXICOLOGY: NA

VI. CARCINOGENICITY: NA

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

The following Reproductive and Developmental Toxicology report was not reviewed as it previously reviewed.

Effect of inhaled fluticasone propionate on pregnant AHA rats and their progeny in vitro, No. WPT/93/602, (See review of Shannon Williams, Ph.D., IND 53,502: Submission date: 6/18/97, Review date, 9/12/97).

VIII. SPECIAL TOXICOLOGY STUDIES:NA

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Fluticasone propionate is a potent fluorinated glucocorticoid. Unlike other corticosteroids, fluticasone propionate increases sodium and potassium urinary excretion. Safety pharmacology studies indicate no potential adverse effects. Orally in mice, fluticasone propionate was not

bioavailable. In rats, the bioavailability by the intranasal route was comparable to the inhaled route in humans. Rats, dogs and humans were similar as they show a high degree of protein binding and a low degree of binding to the red blood cells. In mice, rats, dogs and humans, fluticasone propionate undergoes hydrolysis to the non-toxic -COOH derivative. Excretion of unchanged fluticasone propionate and its metabolites were fecal.

In acute toxicity studies in mice, rats and dogs, the manifestations were similar to those seen with glucocorticoids, i.e., weight loss, decreased thymus weight and/or decreased cortisol levels. By the oral route, fluticasone propionate was not toxic in rats and mice. Juvenile rats were markedly more sensitive by the subcutaneous than the oral route. This was attributed to the high first pass metabolism. By the s.c. route, mice showed cardiac inflammation. In multidose and long-term inhalation studies, when administered as a dry powder or as a metered dose inhaler using a mixture of two chlorofluorocarbon propellants (CFC) to rats, fluticasone propionate produced the classical glucocorticoid effects. There were hair loss, decreased food consumption and decreased lymphocyte levels, hyperglycemia, increased liver and kidney weights, decreased adrenal and spleen weights and histological changes in the liver, thymus and spleen. Similar findings were seen in multidose and long-term inhalation studies in dogs. In the long-term study, the dogs showed lung inflammation due to local irritation and infection due to the compromised immune system.

Multidose toxicity studies were conducted in rats and dogs whereby fluticasone propionate was delivered by the propellant, HFA 134a. The HFA 134a/fluticasone propionate formulations used in these studies were the 22 mcg and 44 mcg of fluticasone propionate per actuation. In a 13-week study in adult rats, fluticasone propionate (5.4, 8.2 and 84.1 µg/kg) was administered as a MDI in which the propellant was HFA 134a and a comparison was made with fluticasone propionate (77.1 µg/kg) administered as a MDI in which the propellant was a mixture of two chlorofluorocarbons (CFC). Particle size was not determined to estimate lung deposition. Serum corticosterone levels were suppressed in a dose-related manner. The characteristic steroidal responses and pharmacokinetics of fluticasone propionate administered with HFA 134a were comparable to those of fluticasone propionate administered with CFC suggesting that the bioavailability of fluticasone propionate with both propellants was comparable. In a 13-week inhalation toxicity study in adult dogs, doses of 10, 24 and 71 µg/kg of fluticasone propionate delivered with the HFA134a propellant were tested. Particle size was not reported to estimate lung deposition. Systemic effects characteristic of glucocorticoids were seen. However, histopathological changes occurred in the carina and lungs at 24 and 71 mcg/kg. They included hypertrophy, and hyperplasia of the carina and hypertrophy and inflammatory exudate in the bronchioles, bronchial fibrosis, and decreased goblet cells indicating an inflammatory response. To determine whether these histopathological changes were due to the propellant, HFA, a second 13-week inhalation study was conducted in which the response to 8 and 77 mcg/kg of fluticasone propionate administered with the HFA propellant was directly compared with the response to 7 and 64 mcg/kg of fluticasone propionate administered with the CFC propellant. Particle sizes (for HFA vs µg for the CFC formulation) were comparable indicating that the lung deposition for both formulations was approximately 20% of the administered dose. There was no difference in the systemic exposure between the two formulations although the glucocorticoid effects of fluticasone propionate were slightly higher with the CFC formulation. The only respiratory histopathology for both formulations containing fluticasone propionate showed slight

bronchitis in the lungs and carina suggesting comparable local respiratory toxicity with the two formulations.

Toxicology studies were conducted in juvenile dogs. In a preliminary 4-week study in 10-week old dogs, only one dose was tested (81 mcg/kg for M and 101 mcg/kg for F) with no corresponding control animals. No obvious toxicity was noted, and there were plasma levels indicative of systemic absorption. In a 7-week pilot study in 2-week old dogs, the inhalation doses tested were 5, 15 and 25 mcg/kg. From the particle size, approximately 20% of the dose was deposited in the lungs. In both sexes, adrenal atrophy and decreased response to ACTH occurred, characteristic of a glucocorticoid effect. In the HD M, there was a decrease in width of the 20th tracheal ring indicating decreased development. The NOAEL was 5 mcg/kg. In a one-year single inhalation dose study in 10-week old juvenile dogs, the effect on tracheal ring development was confirmed as there was a decrease in the size of several tracheal rings in both sexes. However, there was no disorientation of the tracheal rings to be clinically concerned. The initial dose (126-140 µg/kg) was toxic requiring the dose to be lowered after week 8 to 25 µg/kg. Toxicity seen was umbilical hernias, abdominal distension, hair loss, excessive tearing and changes in the thymus, adrenals, spleen and liver. In addition to the effect on tracheal ring development, there were pathologic changes in the larynx, carina and lungs.

In the inhalation toxicology studies submitted in this NDA, the HFA formulations used were the 22 mcg and 44 mcg fluticasone propionate strength products. The 220 mcg strength product that will be marketed was tested in animals in NDA21-254 (Reviewer: L. Sancilio; Date of Review: 10/19/01). It was used in a 13-week study in rats (lung deposition dose of fluticasone propionate: 75.1 mcg/kg) and in a pilot 14-day study in dogs (daily estimated combination inhalation doses: fluticasone propionate, 622 mcg/kg and salmeterol, 143 mcg/kg). In both studies, other than the classic glucocorticoid effects, no compound-related local toxicity in the respiratory tract was seen indicating that the 220 mcg strength fluticasone propionate product was not locally toxic to the respiratory tract.

Fluticasone propionate was not genotoxic or mutagenic. In the carcinogenicity studies in rats and mice, fluticasone propionate was not tumorigenic. In reproductive studies when fluticasone propionate was administered by the subcutaneous route, fertility was not affected, but fetotoxicity and teratogenicity was seen in mice, rats and rabbits. No teratogenicity was seen at inhalation doses up to 68.7mcg/kg in rats and at oral doses up to 300 mg/kg in rabbits. Very little fluticasone propionate crosses the placenta of rats and rabbits following oral administration. Radioactivity was found in the milk of lactating rats following subcutaneous administration of tritiated fluticasone propionate.

Conclusions: Fluticasone propionate, a glucocorticoid, administered by inhalation using HFA134a as the propellant produced systemic effects characteristic of its class. There was no difference in the response between the fluticasone propionate- HFA 134a and fluticasone propionate-CFC formulations.

General Toxicology Issues: None.

Recommendations:

Approval of this NDA is recommended.

Labeling with basis for findings:

The following changes (**BOLD**) are recommended since this data was not included in the proposed label or the information more clearly identifies the safety margin.

Pregnancy: Teratogenic Effects: Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively, (less than the maximum recommended daily inhalation dose in adults on a mcg/m²), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocelle, cleft palate, and retarded cranial ossification. **No teratogenicity was seen in the rat at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m²).**

OVERDOSAGE

The oral and subcutaneous median lethal doses in rats and mice were >1000 mg/kg — **4600 and 2300** times the maximum human daily inhalation dose based on mg/m², respectively)

X. APPENDIX/ATTACHMENTS:

Addendum to review:

Other relevant materials:

Attachments

Review of IND 53,502 by Shannon Williams, Ph.D., Submission date: 6/18/97 Review date, 9/12/97

Review of IND 53,502 by W. Mark Vogel, Ph.D., Submission date: 8/18/97 Review date, 8/5/98.

Review of IND 53,502 by W. Mark Vogel, Ph.D., Submission date: 8/21/98 Review date, 11/16/98.

Review of NDA 20-770 by L. Sancilio, Ph.D., Submission date: 9/26/96 Review date, 6/2/97.

Any compliance issue: None.

The ratios of the preclinical dose to the maximum human inhalation dose based of surface areas

Drug: **Fluticasone propionate HFA**

	age	mg/dose	# daily		kg	mg/kg	factor	mg/m ²
			doses	mg/day				
Pediatric				0	18	0.0190	25	0.48
Adult	>12	0.22	8	1.76	50	0.0352	37	1.30

	route	mg/kg/d	conv.		Dose Ratio		Rounded Dose Ratio	
			factor	mg/m ²	Adults	Children	Adults	Children
<u>Carcinogenicity:</u>								
Mouse	p.o.	1	3	3	2.30	6.32	2	6
rat	inh	0.057	6	0.342	0.26	0.72	1/4	1/1
Hamster			4	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
<u>Reproduction and Fertility:</u>								
Mouse			3	0	---	N/A	---	N/A
rat	s.c.	0.05	6	0.3	0.23	N/A	1/4	N/A
rat	s.c.	0.01	6	0.06	0.05	N/A	1/22	N/A
rat	inh	0.0687	6	0.412	0.32	N/A	1/3	N/A
<u>Teratogenicity:</u>								
Mouse	s.c.	0.045	3	0.135	0.10	N/A	1/10	N/A
rat	s.c./p.o.	0.1	6	0.6	0.46	N/A	1/2	N/A
Rabbit	s.c.	0.004	12	0.048	0.04	N/A	1/27	N/A
Rabbit	p.o.	0.3	12	3.6	2.76	N/A	3	N/A
Mouse	s.c.	0.1	3	0.3	0.23	N/A	1/4	N/A
<u>Overdosage</u>								
Mouse	s.c.	1000	3	3000	2303.44	6315.79	2300	6300
Mouse			3	0	---	---	---	---
rat	p.o.	1000	6	6000	4606.88	12631.58	4600	13000
rat			6	0	---	---	---	---

**DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Review**

IND No. : 53,502

Submission date: June 18, 1997

Received at HFD 570: June 20, 1997

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

Reviewer: Shannon Williams, Ph.D.

Date Review Completed: 9/12/97

Sponsor: GlaxoWellcome

Drug Name: Fluticasone Propionate/GR106642X Inhalation Aerosol

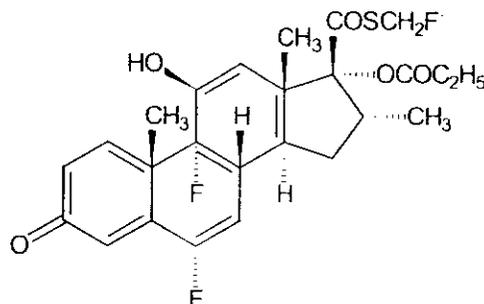
Class: Fluticasone Propionate: Inhaled Corticosteroid
GR106642X: HFA-134a, — ropellant

Chemical Name:

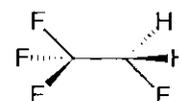
Fluticasone Propionate: S-FLuotomethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate

GR106642X: 1,1,1,2-tetrafluoroethane

Chemical Structure:



Fluticasone Propionate



GR106642X
(HFA-134a)

Molecular Weight:

Fluticasone Propionate: 500.6

GR106642X: 102.0

IND53,502

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Clinical indication:

Related INDs/NDAs/DMFs:

IND No. 44,090; Fluticasone propionate multidose inhaler

IND No. 28,636; Fluticasone Propionate aqueous nasal spray

IND No. 40,142; Fluticasone Propionate Rotodisk

NDA No. 20,548; Flovent inhalation aerosol

NDA No. 20,549; Fluticasone Propionate Rotodisk inhalation powder

**NDA No. 20,770; Fluticasone Propionate Rotodisk inhalation powder-Pediatric application
DMF**

Proposed Clinical Protocol: A multicenter, randomized, double-blind, placebo-controlled comparative trial of fluticasone propionate (440 mcg BID or 880 mcg BID) versus placebo administered via a metered dose inhaler in propellant 11/12 or GR106642X in adolescent and adult corticosteroid-dependent asthmatics.

***Objective:* Compare the doses-related efficacy and safety and the health-related quality of life (HQLQ) of Fluticasone propionate (440 mcg BID and FP 880 mcg BID) utilizing the 220 mcg formulation administered by pressurized metered dose inhaler propelled by 11/12 or GR106642X**

***Design:* Randomized, double-blind, parallel-group, placebo-controlled trial**

***Dose/Frequency:* 440 mcg BID or 880 mcg BID (ex-actuator doses) Ex valve doses are 500 mcg and 1000 mcg)**

***Duration of clinical study:* 16 week treatment period**

***Age of patient population:* 18-46 years**

***Number of Patients:* Total of 165 (male or female asthmatic patients > 12 years of age, corticosteroid dependent for the last 6-months)**

**Preclinical Studies Submitted and Reviewed Herein:
SUBCHRONIC TOXICOLOGY:**

1. **Fluticasone Propionate/GR106642X: 13-week Inhalation Toxicity/Toxicokinetic Study in Rats (Report No. WPT/94/028, Vol. 6)**
2. **Fluticasone Propionate/GR106642X: 13-week Inhalation Toxicity/Toxicokinetic Study in Dogs (Report No. WPT/92/425, Vol.8)**

REPRODUCTIVE TOXICOLOGY:

Fluticasone Propionate/GR106642X: Effects of inhalation administration on Pregnant Allen and Hanbury's Albino (AHA) rat and their Progeny in utero (Report No. WPT/93/602, Vol.11)

Studies Not Reviewed in this IND:

1. **14-week Inhalation Toxicity/Toxicokinetic Study in Rats (Report No. WPT/93/088)**
In this initial study GR106642X Control animals showed plasma concentrations of fluticasone propionate rendering the study to be of questionable validity. This study was therefore repeated (See Report No. WPT/94/028). Both the initial and repeat studies showed similar toxicity profiles. Thus, only the repeat study (Report No. WPT/94/028) is reviewed herein.
2. **52-week inhalation Toxicity study in Juvenile Dogs (Report No. WPT/95/096 NDA 20-770, Submission Dated 9/26/96) Previously reviewed by Dr. Lawrence F. Sancilio in a pharmacology review of NDA 20-770 Dated June 5, 1997.**
3. **Fluticasone Propionate: Micronucleus Tests in Mice after oral administration (M10680, or subcutaneous administration (M10726) Assay with Fluticasone Propionate (Report No. WPT/93/569, IND 44,090, Submission dated 9/12/94). Previously reviewed by Dr. Lawrence F. Sancilio in a pharmacology review of IND 44,090 Dated February 14, 1995.**

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

SUBCHRONIC TOXICOLOGY

Fluticasone Propionate/GR106642X: 13-week Inhalation Toxicity/Toxicokinetic Study in Rats (Report No. WPT/94/028 Vol 6)

Study Number: R20200

Testing Lab: Glaxo Group Ltd.

Study Dates: October 18, 1993 through June 15, 1994

Test Article: CCI18781 in GR106642X (alternative propellant)

Study Animals: — Wistar rats, 6-8 weeks old, Males: 149.3-354.4 g and Females: 155.0 to 255.3 g

GLP: A statement of compliance with the current FDA Good Laboratory Practice Regulations (21 CFR Part 58) was included..

Methods: Fluticasone Propionate (CCI18781) in propellant GR106642X) was administered to groups of rats (20/sex/group) using snout only at mean chamber concentrations of 0 (GR106642X propellant control), 0.44, 0.49 and 2.21 mcg/liter (administered for 20 min/day preceded by 40 min of air). Not considering deposition factors, estimated daily doses were: 0

(propellant control), 0.0054, 0.0182, 0.0841 mg/kg and were calculated using the following formula:

$$\text{Dose to animal (mg/kg/day)} = \frac{\text{RMV} \times \text{T} \times \text{C}}{\text{BW} \times 1000}$$

Where T = Time of exposure (min/day); C = Chamber concentration ($\mu\text{g/L}$); BW = Body weight (g); and $\text{RMV} = 4.19 \times \text{BW}^{0.66}$ = Respired minute volume.

Separate groups of rats (6/sex/group) were likewise treated with the aforementioned doses of fluticasone in the HFA propellant, with an additional group also given the high dose of CCI18781 (2.21 mcg/liter; estimated daily dose of 0.0771 mg/kg) in the CFC propellant P11/P12. These latter groups of rats were used for comparison of plasma CCI18781 and serum corticosterone levels. Rats were killed for post mortem studies either at the end of 91 days of dosing (12 rats/sex/group) or at the end of a recovery period of 31-33 days (8 rats/sex/group). The basis of dose selection was not indicated. The following parameters were determined:

Clinical Observations: 2x daily

Mortality: 2x daily

Body weights: Pretreatment, Day 0 and weekly

Food Consumption: During the final week of the pretreatment period and Weekly through the end of the recovery period.

Ophthalmoscopy: All rats days -7/-6 and on day 81 in GR106642X propellant control and high dose groups.

Hematology: Venous samples were collected on Day 32 (10 rats/sex) and Day 79/80 (all surviving rats) of treatment, at sacrifice (Day 91-94), Day 114 of the recovery period and at the end of the recovery period Days 121-123.

Clinical chemistry: Venous samples were collected on Day 32 (10 rats/sex) and Day 79/80 (all surviving rats) of treatment, at sacrifice (Day 91-94), Day 114 of the recovery period and at the end of the recovery period Days 121-123

Hearing tests: All rats days 86/87

Serum Corticosterone: Venous blood samples (approximately 0.8 ml) were collected from all satellite rats on Days -5, 7, 37, 91 of treatment and on Days 105 and 123 of the recovery period.

Plasma Drug Levels: Venous blood samples (approximately 0.8 ml) were collected at predose and 10 min, 1.0 hr, and 24 hr (Day 1 only) after dosing from 2 rats/sex from all satellite rats on days 0/1, 16, 30, and 84. Plasma levels of CCI18781 were determined using radioimmunoassay with a calibration curve in the concentration range 0 - $\mu\text{g/ml}$.

Urinalysis: 16 hr samples collected on Days 28 (10 rats/sex) and 84/85 of treatment and on day 112 of recovery.

Necropsy: Complete gross examinations were conducted on rats which: experienced intercurrent deaths, were sacrificed after 91 days of treatment (12 rats/sex/group), or were sacrificed at the end of the recovery period (8/sex/group) underwent. Rats in the high dose CFC propellant group were sacrifice at the end of the recovery period (Day 123) without necropsy.

Organ Weights: Organ weights were determined for lungs, liver, heart, adrenals, thymus, kidneys, brain, spleen, pituitary, prostate, ovaries, testes, and uterus.

Histopathology: Histological exams conducted on rats at the end of the treatment period were as follows: complete histological examinations were conducted for all intercurrent deaths and for control and high dose rats, whereas exams for rats in the low and intermediate doses were limited to thymus, adrenal, spleen and lymph nodes (cervical and mesenteric). Exams conducted on rats at the end of the recovery period were limited to thymus, adrenal, spleen and lymph nodes (cervical and mesenteric). As a rule, if less than complete histological examinations are conducted at the low and mid doses, these examinations are required to include all target organs of toxicity identified at the high dose. The present protocol deviated from this rule in that it prespecified a limited number organs which were to be examined at the low and mid doses. However, in this case those organs examined captured all the target organs of toxicity identified at the high dose, thus allowing the study to be acceptable.

Results:

Mortality: Six rats died or were killed during the treatment period (3 females were found dead in the exposure tubes (Two at the high dose on day 2 and 1 at the mid dose on day 35). Three other rats, 2 males and one female were killed (one control male not eating well due to a broken incisor on Day 4, one high dose male on day 16 due to excessive blood in urine and an enlarged liver and a high dose female killed for humane reasons due to an exposure tube damaged eye on Day 87), respectively. All deaths were considered to be due to the restraint procedure or incidental and not due to drug exposure.

Clinical Observations: Clinical signs of toxicity were limited to an increased incidence of hair loss in rats at the high dose (5 and 14 of 20 affected males and females, respectively versus 0 and 3 in the HFA propellant control group). By the end of the recovery period regrowth and fewer areas of loss observed, suggesting the effect was reversible.

Ophthalmoscopy: No treatment related ophthalmic effects were observed. Two rats, 1 low dose male and a mid dose female showed atrophy of the eye following orbital bleeding. Atrophy of the eye occasionally occurs following orbital sinus puncture in rats.

Body Weight: Dose-related reductions in Day 86 mean body weights were observed in rats at the low (2%, both sexes), intermediate (2 and 10% in males and females, respectively) and high doses (18% both sexes), relative to controls. Comparable reductions in mean body weights were observed in rats in the Satellite high dose HFA groups (21 and 20 % in males and females, respectively) and in the High dose CFC treated rats (14 and 28% in males and females, respectively). Effects on body weights were reversible, following cessation of treatment.

Food and Water Consumption: Dose-dependent reductions in food consumption was observed in all drug treated groups (7-19%). Comparable reductions in food consumption were also observed in the satellite high dose HFA (23-13% in males and females, respectively) and high dose CFC (14 and 28% in males and females, respectively) groups. Effects on food consumption were reversible following cessation of dosing.

Hematology: Hematological changes evident after 79 days of dosing are presented in Table 1 below.

Table 1. Changes in Hematological Parameters in Rats Treated with Fluticasone for 32 Days* or 79 Days.

Fluticasone Propionate (FP)+GR106642X (HFA-134a)								
FP= 5.4 µg/kg			FP=18.2 µg/kg			FP= 84.1 µg/kg		
(Day 79)	♂	♀	(Day 79)	♂	♀	(Day 79)	♂	♀
Hemoglobin	---	---	Hemoglobin	12%	---	Hemoglobin	16%	13%
Hematocrit	12%	---	Hematocrit	12%	---	Hematocrit	16%	13%
Red blood cells	13%	---	Red blood cells	13%	---	Red blood cells	19%	13%
Thrombotest Time	19%	---	Thrombotest Time	110%	15%	Thrombotest Time	115%	14%
White blood cells	114	---	White blood cells	122%	113%	White blood cells	142%	128
Neutrophils	%	---	Neutrophils	---	116%	Neutrophils	119%	%
Lymphocytes	---	---	Lymphocytes	132%	123%	Lymphocytes	164%	159
Eosinophils	120	---	Eosinophils	136%	---	Eosinophils	150%	%
Basophils.	%	---	Basophils.	153%	150%	Basophils.	176%	162
Large unstained cells	125	---	Large unstained cells	---	---	Large unstained cells	---	%
Fibrinogen	124	---	Fibrinogen	---	---	Fibrinogen	115%	132
	%	---						%
	---							167
	---							%
								131
								%

n=20 rats/sex/group; (---) values not significantly different from controls

Values are expressed as % change relative to respective values in the HFA placebo group on Day 79 of treatment.

The data in Table 1 show treatment related changes which included: small dose related increases in hemoglobin concentration, hematocrit and total erythrocyte counts; a general dose-related reduction in the total white blood cell counts due to dose related reductions in the mean total lymphocytes, eosinophils and basophils; and a corresponding increase in mean total neutrophil counts. The aforementioned effects are consistent with those expected following administration of a corticosteroid. Other observed effects of which the toxicological significance is unknown included: mild reductions in Thrombotest clotting times in males in all fluticasone-treated groups, increased fibrinogen in males at the high dose, and increased numbers of large unstained cells in females at the high dose.

Clinical Chemistry: Table 2, (below) shows the alterations in clinical chemistry observed on day 79/80.

Table 2. Changes in Clinical Chemistry in Rats Treated with Fluticasone for 32 Days* or 79 Days.

Fluticasone Propionate (FP)+GR106642X (HFA-134a)								
FP= 5.4 µg/kg			FP=18.2 µg/kg			FP= 84.1 µg/kg		
(Day 79)	♂	♀	(Day 79)	♂	♀	(Day 79)	♂	♀
Triglycreides*	↑11%	↑38%	Triglycreides*	↑12%	↑53%	Triglycreides*	↑28%	↑80%
Serum Bilirubin*	---	---	Serum Bilirubin*	↑23%	↑22%	Serum Bilirubin*	↑30%	↑40%
Serum Bilirubin	---	---	Serum Bilirubin	---	---	Serum Bilirubin	↑11%	↑18%
Serum Glucose	---	---	Serum Glucose	---	↑12%	Serum Glucose	---	↑12%
Urea	↑18%	---	Urea	↑19%	↑12%	Urea	↑21%	↑18%
Total Prot.	↑3%	---	Total Prot.	↑4%	---	Total Prot.	↑19%	---
Albumin	↑2%	---	Albumin	↑2%	---	Albumin	↑15%	---
Creatinine	---	---	Creatinine	↑9%	---	Creatinine	↑14%	---
Cholesterol	---	---	Cholesterol	---	---	Cholesterol	↑20%	---
Serum LDH	---	---	Serum LDH	---	---	Serum LDH	↑39%	---
Serum ALN	---	---	Serum ALN	---	---	Serum ALN	---	↑25%

n=20 rats/sex/group; --- values not significantly different from controls

Values are expressed as % change relative to respective values in the HFA placebo group on Day 79 of treatment, except those parameters marked with an astric (*) which represent measurements made on Day 32 of treatment.

Table 2 above shows that treatment-related changes in clinical chemistry which included a dose-related increase in group mean serum bilirubin (observed beginning day 32 at the mid and high dose), urea, total protein, and albumin. Dose-dependent increases in triglycerides were also observed after 32 days of treatment, but were not evident on day 79. Slight reductions in serum sodium observed in females from all drug treated groups (from control values of 145.25 mmol/l down to 143.87 mmol/l at the high dose) were considered to be of minor toxicological significance. Effects on serum bilirubin and urea were not evident by day 112 of the recovery period, whereas total protein and albumin had rebounded being slightly reduced by day 14 of the recovery period. Overall the aforementioned changes in clinical chemistry values are consistent with those expected following administration of a corticosteroid.

Urinalysis: Significant treatment-related changes in urinalysis parameters were observed at the high dose and included reduced urine volume (40%) in high dose females (associated with reduced water consumption 46%); increased sodium (39 and 15% in high dose males and females, respectively) and reduced potassium (33 and 27% in high dose males and females, respectively). During the recovery period urinary volume increased and potassium excretion rebounded, with increases in both, relative to the HFA vehicle controls. These changes in urine electrolytes may reflect reductions in the circulating levels of corticosterone which possesses mineralocorticoid activity (i.e. acts at the nephron to promote of reabsorption of sodium at the expense of potassium).

Organ Weights: Treatment related alterations in organ weights occurred in animals at the intermediate and high doses and are tabulated in Table 3 (below).

Table 3. Organ weight changes in rats at the mid and high doses following 91 days of treatment (n=12 except for high dose males, where only 11 animals were examined).

Fluticasone Propionate (FP)+GR106642X (HFA-134a)									
Mid dose FP=18.2 µg/kg					High dose FP= 84.1 µg/kg				
♂		♀			♂		♀		
Organ	Absolute Wt.	Relative Wt.	Absolute Wt.	Relative Wt.	Organ	Absolute Wt.	Relative Wt.	Absolute Wt.	Relative Wt.
Body Wt.	12%	NA	110%	NA	Body Wt.	118%	NA	118%	NA
Lung	---	---	---	19%	Lung	113%	[14%]	[18%]	110%
Heart	---	---	---	---	Heart	[17%]	112%	[15%]	120%
Thymus	---	---	---	---	Thymus	137%	---	160%	150%
Spleen	---	19%	---	---	Spleen	118%	---	121%	---
Liver	---	---	---	---	Liver	---	125%	---	115%
Adrenals	18%	110%	---	114%	Adrenals	---	---	122%	---
Kidneys	---	---	[119%]	120%	Kidneys	16%	128%	16%	125%
Pituitary	---	---	NA	NA	Pituitary	---	---	[116%]	122%
Testes	NA	NA	---	---	Testes	---	119%	NA	NA
Ovaries	---	---	---	---	Ovaries	NA	NA	[119%]	145%
Brain	---	---	---	---	Brain	---	119%	---	119%

Values are expressed as % change relative to respective values in the HFA placebo group
[values in brackets not statistically significant]; NA = nonapplicable

Table 3 shows expected corticosteroid related changes in organ weights which included: reductions in absolute weights for adrenals, spleen, and thymus. The statistically significant increases in relative weights for brain, heart, testes, ovaries and pituitary (females) may be due in part to reduced body weights, although small increases in absolute weights for ovaries (females at the high dose) and pituitary (females at all dose) suggest a treatment related component. Other changes in organ weights including reduced absolute weights for heart and lungs (in high dose males) appeared related to alterations in body weights, since the relative weights for both organs were increased. Finally, the reasons for increases in absolute and relative weights for kidney (intermediate and high doses) and relative weights for liver are not clear considering the observed reductions in body weights.

Gross Pathology: Gross pathological effects were limited to reduction in the size of the thymus in 1 of 11 males and 2 of 12 females at the high dose. The appearance of other gross pathological effects appeared sporadic and unrelated to drug treatment.

Histopathology: A tabulated summary of treatment related histological findings observed in rats treated with Fluticasone Propionate (FP)+GR106642X (HFA-134a) the high dose (84.1 µg/kg) is presented in Table 4 (succeeding page).

Table 4. Treatment-Related Histological changes in Rats Treated with Fluticasone Propionate (FP)+GR106642X (HFA-134a) at the High dose (84.1 µg/kg).

Fluticasone Propionate (84.1 µg/kg)		
(Day 79)	♂	♀

Thymic atrophy (cortical lymphocyte depletion)	1/11	4/12
Spleen (white pulp depletion)	1/11	8/12
Cervical Lymph node, Lymphocyte Depletion	3/11	0/12
Mesenteric Lymph node, Lymphocyte Depletion	4/9	3/12
Recovery Animals		
Spleen (white pulp depletion)	0/8	3/8

Briefly the treatment-related histological findings were consistent with those expected following administration of corticosteroids. In animals at the high dose which were sacrificed at the end of the treatment period histological findings included: Thymic atrophy, with cortical lymphocyte depletion; depletion of splenic white pulp and lymphocyte depletion of the cervical and mesenteric lymph nodes. In rats sacrificed at the end of the recovery period, histological effects were limited to depletion of the white pulp of the Spleen was still evident in 3 of the 8 high dose females observed. No histological correlates associated with the **increases in absolute and relative weights for kidney (intermediate and high doses) and relative weights for liver** were observed.

Serum corticosterone and Plasma Fluticasone Levels: Tables 5 and 6 (below) present a tabulated summary of plasma fluticasone levels and serum corticosterone levels, respectively.

Table 5. Plasma Fluticasone levels on Days 1, 16, 30 and 84 of treatment, measured at predose, 10 min, 1 hr, and/or 24 hr (Day 1 only) after dosing in the rats treated with either the HFA or the CFC formulations.

Day	Time	Fluticasone Propionate Plasma concentrations			
		5.4 + HFA pg/ml	18.2 + HFA pg/ml	84.1 + HFA pg/ml	77.1 + CFC pg/ml
1	Predose	<250	<250	<250	<250
	10 min	<500	542-646	<500-1227	<500-844
	1 hr	<500	<500-732	1293-1874	712-1101
	24 hr	<250	<250	<250-294	<250
16	Predose	<500-710	<500	<500	<500-525
	10 min	<500	<500	<500-1749	617-1381
	1 hr	<500	<500-543	1219-1950	503-1011
30	Predose	<500	<500	<500	<500
	10 min	<500	<500-1107	532-1258	679-1856
	1 hr	<500	<500-545	950-2117	976-1433
84	Predose	<500	<500	<500	<500
	10 min	<500-543	<500-996	740-1555	865-2086
	1 hr	<500	<500-822	1481-2234	1066-1618

The data in table 5 show that levels of CCI18781 (fluticasone propionate) were detected in all dose groups indicative of systemic exposure. Plasma levels at the low dose were barely detectable and increased with increasing dose with the HFA formulation. There were no discernable differences between the levels of fluticasone detected following administration

of the High dose HFA formulation relative to those detected following administration of comparable dose in the P11/P12 CFC formulation, suggesting little differences in the exposure between the two formulations. In addition, no sex-related differences were detected with either formulation.

Table 6. Changes in Serum Corticosterone levels (nmol/L) in Rats Measured after 91 Days of administration of Fluticasone Propionate in the HFA formulation or in the P11/P12 CFC propellant formulation.

Dose ($\mu\text{g}/\text{kg}$)		♂	♀
0.00 Vehicle Control GR106642X	Corticosterone (PD)	447.0	1087.0
	Corticosterone (30 min)	1441.3	2229.0
5.4 HFA	Corticosterone (PD)	345.0	1276.2
	Corticosterone (30 min)	1541.2	2368.2
18.2 HFA	Corticosterone (PD)	245.7	986.8
	Corticosterone (30 min)	1419.7	2521.0
84.1 HFA	Final body wt.(day 86)	121%	120%
	Food consumption	123%	113%
	Corticosterone (PD)	59.3	82.8
	Corticosterone (30 min)	1213.5	2270.8
77.1 CFC	Final body wt.(day 86)	114%	128%
	Food consumption	115%	124%
	Corticosterone (PD)	62.6	245.0
	Corticosterone (30 min)	1355.2	2065.5

Serum Corticosterone levels measured on Day 91 at either PD Prior to 125 μg Synacthen injection or at 30 min post Synacthen injection

The data in Table 6 show that fluticasone propionate + GR106642X (HFA formulation) produced dose-dependent reductions in mean serum basal corticosterone levels to a maximum of 87-92% at the 84.1 mcg/kg high dose high. Maximum levels achieved following stimulation with synacthen were less so inhibited, with only 16 and 2% reductions seen in males and females at the high dose, respectively. Rats administered fluticasone at the 77.1 mcg/kg dose in the CFC formulation showed reductions in basal corticosterone levels (86 and 77%) which were comparable to those observed using the HFA formulation. Likewise, only slight reductions in synacthen stimulated corticosterone levels (6-7%) were observed following administration of the CFC formulation. Finally, data presented in Table 6 show that fluticasone propionate produced comparable reductions in body weight gains (14-28%) and food consumption (15 to 24%), whether administered as the HFA or CFC formulation.

In conclusion, rats administered Fluticasone propionate + GR106642X (HFA formulation) via inhalation exhibited toxicological effects consistent with the anticipated response to corticosteroids in general and similar to those observed in a previous 3-month inhalations toxicity study with fluticasone formulated with the CFC P11/P12 propellants (i.e. hair loss, dose-related reductions in body weight gain, alterations in hematological (increased

red blood cell parameters, reductions in total leukocytes due mainly to reductions in neutrophils, lymphocytes and eosinophils) and clinical chemistry parameters (increases in serum bilirubin, urea, total protein, and albumin). Target organs of toxicity included: thymus (atrophy and cortical lymphocyte depletion), spleen (white pulp depletion), and lymph nodes (lymphoid depletion in the cervical and mesenteric lymph nodes). Effects which were generally reversible except depletions of the white pulp of the Spleen which was still evident in 3 of the 8 high dose females observed following cessation of dosing for 31-33 days. Although a direct comparison of the toxicological effects between fluticasone formulations using the HFA vs the CFC propellants was not incorporated into the study, plasma levels of fluticasone, reductions in body weights, and suppression of corticosterone levels were comparable following administration of fluticasone propionate whether formulated in the HFA or the CFC P/11/P12 propellants. Thus, the available data, suggests that administration of fluticasone formulated with the HFA propellant does results in comparable systemic exposure and effects consistent with that observed with the currently approved CFC formulation.

Fluticasone Propionate/GR106642X: 13-week Inhalation Toxicity/Toxicokinetic Study in Dogs (Report No. WPT/92/425, Vol. 8)

Study Number: D13370

Testing Lab:

Study Dates: June 18, 1992 through May 17, 1994

Test Article: CCI18781 in GR106642X (alternative propellant), Batch No U92/004A
CCI18781 in P11/P12 (CFC propellant), Batch No. R9634/001

Study Animals: Pure bred beagle dogs, 16-20 weeks old, 6.7 to 10.1 kg

GLP: A statement of compliance with the current FDA Good Laboratory Practice Regulations (21 CFR Part 58) was included..

Methods: Futicasone Propionate (CCI18781) in propellant GR106642X) was administered to groups of dogs via an oropharyngeal tube with 4, 10, and 30 actuations of a metered dose inhaler designed to deliver 47.6 mcg/metered dose (1/2 of total daily dose administered 2x daily for 13 weeks). The aforementioned estimated total daily doses were calculated using the following formula:

$$\text{Dose to animal (mcg/day)} = N \times 47.6 \text{ mcg /metered dose} \times Z$$

Where N = number of metered doses/day and Z = the retained drug (total dose administered - that recovered from the dosing apparatus; mean = 41%; range 34-46%).

Mean estimated daily doses were 0 (propellant control 8/sex/group), 78.1 (6/sex/group), 195.2 (6/sex/group), and 585.5 mcg/day (8/sex/group); equivalent to approximately 10, 24, and 71 mcg/kg, based on an initial body weight of 8.2 kg.

Separate groups of dogs (2/sex/group) were likewise treated with fluticasone, formulated in the P11/P12 CFC propellant, at a daily dose of 628.3 mcg/day or 77 mcg/kg, based on an initial body weight of 8.2 kg. These latter groups of dogs were used for absorption studies, with observations

limited to clinical signs, changes in body weights and food consumption. Dogs were killed for post mortum studies either at the end of 2 weeks (2 dogs/sex/group) following 13-weeks of dosing (4/sex/group), and the remaining 2 dogs/sex at the in the control and high dose group killed at the end of an additional 4-week post dosing recovery period. The basis of dose selection was not indicated. The following parameters were determined:

Clinical Observations: Daily, with careful external examinations weekly

Mortality: Daily

Body weights: Weekly beginning 2 weeks prior to the start of the study

Food Consumption: Daily.

Electrocardiography: HFA dogs Weeks: -2, 2, and 13

Ophthalmoscopy: HFA dogs Weeks: 2 and 13

Hematology: Venous samples from HFA dogs Weeks: -2, 3, 12, and 17 (week 4 of recovery)

Clinical chemistry: Venous samples from HFA dogs Weeks: -2, 3, 12, and 17 (week 4 of recovery)

Plasma cortisol with Synacthen challenge: HFA groups, measured before and at 1.5 hr after Synacthen at Predose and weeks: 3, 5, and 12 of dosing, and Week 4 of recovery.

Plasma Drug Levels: Blood samples (approximately 4 ml) were collected from 2 dogs /sex at predose and at various time points up to 24 hrs post dosing during weeks 3, 6, and 13 of dosing. Plasma levels of CCI18781 were determined using radioimmunoassay with a calibration curve in the concentration range of $1 - 100$ pg/ml.

Urinalysis: 16 hr urine samples were collected on from HFA dogs Weeks: -2, 3, 12, and 17.

Necropsy: Complete gross examinations were conducted on all dogs in the HFA groups, whether sacrificed after 16 days of treatment, following 13-weeks of dosing, and at the end of the 4-week post dosing recovery period.

Organ Weights: Organ weights were determined for adrenals, brain, heart, kidneys, liver, lungs, pituitary, prostate, spleen, testes and ovaries, thyroids, and thymus.

Histopathology: Complete histological exams were conducted on all dogs in the HFA groups whether sacrificed after 16 days of treatment and following 13-weeks of dosing. In dogs killed at the end of the recovery period (control and high dose HFA groups), histological examinations were limited to macroscopically abnormal tissues and tissues which showed treatment-related findings in dogs sacrificed after 13-weeks of dosing.

Results:

Mortality: There were no unscheduled deaths.

Clinical Observations: Clinical observations were limited dogs at the high dose given fluticasone formulated in the HFA or CFC propellants which were described as obese (both during treatment and during the recovery period), despite the lower body weight gains in these groups.

Ophthalmoscopy: No treatment related ophthalmic effects were observed.

Body Weight: Fluticasone treatment produced treatment-related suppression of body weight gains were observed in both sexes at the low (22%), Mid (32%), and high doses (27%), as did dogs in the high dose P11/P12 group (13.5%), relative to gains of 3.7 kg in the HFA vehicle control group. Effects on body weights were reversible, following cessation of treatment, with mean weight gains being greater in the High dose HFA dogs relative to vehicle controls.

Food and Water Consumption: No effects on food consumption were observed during the treatment period. However food consumption was reduced in 3 of 4 high dose animals (mean reductions = 23% range = 8-47%) during the recovery period.

Hematology: Hematological changes evident during weeks 5 and/or 12 are tabulated in Table 7 (below).

Table 7. Changes in Hematological Parameters in Dogs Treated with Fluticasone
(Values are expressed as % change from respective HFA vehicle group values during week 12 of treatment)

Fluticasone Propionate (FP)+GR106642X (HFA-134a)								
	FP= -10 µg/kg			FP=-24 µg/kg			FP= -71 µg/kg	
	♂	♀		♂	♀		♂	♀
						Neutrophils*	130%	---
						Lymphocytes*	137%	---
						Lymphocytes	[124%]	[129%]
Eosinophils	170%	---	Eosinophils	1100%	[160%]	Eosinophils	173%	1100%
Prothrombin Time	[116%]	---	Prothrombin Time	[120%]	[112%]	Platelets	121%	133%
						Prothrombin Time	121%	115%

n=4-6 dogs/sex/group; (---) values not comparable to HFA control values.

* Values represent measurements made during week 5 expressed as % change relative to respective values in the HFA placebo group on Day 79 of treatment.

[Values in brackets did not attain statistical significance]

Observed treatment-related hematological effects included reduced eosinophils (all doses), reduced numbers of lymphocytes (high dose dogs weeks 5 and 12 of dosing) and increases in platelet numbers. At the end of the recovery period lymphocyte numbers in high dose dogs remained somewhat lower than controls. Slight increases in platelet numbers was associated with significant reductions in prothrombin times at the high dose. Increased numbers of neutrophils were also seen at week five, but were comparable to vehicle levels by the end of the dosing period and are not considered to be of toxicological significance. In general the aforementioned hematological effects are consistent with the expected effects of high dose corticosteroids and are similar to effects reported previously in dogs treated with fluticasone formulated with the P11/P12 CFC Propellant.

Clinical Chemistry: Table 8, (succeeding page) presents a tabulated summary of the alterations in clinical chemistry observed on day 79/80.

Table 8. Changes in Clinical Chemistry in Dogs Treated with Fluticasone for 12 weeks. (values are expressed as a % change from values in the HFA vehicle control group)

Fluticasone Propionate (FP)+GR106642X (HFA-134a)								
	FP= ~10 µg/kg		FP= ~24 µg/kg		FP= ~71 µg/kg			
	♂	♀	♂	♀	♂	♀		
Total Protein	16%	---	Glucose	---	16%	Glucose	---	115%
Globulin	118%	110%	Total Protein.	111%	14%	Total Protein	111%	119%
Creatinine	---	113%	Globulin	118%	119%	Globulin	---	112%
Alk.Phos.	19%	---	Albumin	---	112%	Albumin	---	112%
AST	---	11%	Creatinine	114%	125%	Creatinine	128%	138%
LDH	---	[1104%]	Alk.Phos.	---	[129%]	Alk..Phos.	1121%	1102%
			AST	125%	---	AST	140%	[123%]
			LDH	---	[195%]	LDH	[180%]	1263%
			Potassium	---	112%	Phosphorus	115%	---
						Potassium	---	119%
						Calcium	---	14%
						Chloride	---	15%
						Cholesterol	147%	173%
Recovery dogs								
						Glucose	15%	13%
						Creatinine	133%	125%
						Alk. Phos.	174%	125%

n = 6-8 dogs/sex/group; --- values not significantly different from controls

[Data in brackets not statistically significant]

The data in Table 8 above show treatment-related changes in clinical chemistry (week 12) which included: slight reductions in plasma glucose (mid and high dose), a dose-related increase in plasma total protein, increased globulin (all doses) and albumin (high dose females), a dose-related reductions in creatinine (all doses), increased alkaline phosphatase (high dose, with a trend for this effect in females at the mid dose), reduced aspartate aminotransferase (mid and high dose), increased lactate dehydrogenase (significant in high dose females); increased cholesterol (high dose). Slight changes in plasma electrolytes (increased potassium and reduced plasma inorganic phosphorus and chloride) at the mid or high dose appeared to either represent trends present at predose and/or fluctuations in control values between time points. In addition, individual electrolyte values were generally within the background range and were thus not regarded as being toxicologically significant.

Dogs at the high dose which underwent the recovery period continued to show slightly lower glucose and creatinine, and elevated alkaline phosphatase. Other changes in clinical chemistry parameters were either completely resolved or in resolution by the end of the recovery period. Overall the aforementioned changes in clinical chemistry values are consistent with those observed previously in dogs following administration of fluticasone formulated with the CFC P11/P12 propellant.

Urinalysis: No toxicologically significant changes in urinalysis parameters were observed.

Organ Weights: Treatment related alterations in organ weights occurred in animals at the intermediate and high doses and are tabulated in Table 9 (below):

Table 9. Organ Weight Changes in Dogs after 13-weeks of Inhalation treatment

Fluticasone Propionate (n=4/group)	78.1 µg/day @10 µg/kg HFA-134a 6/sex (% Change)		195.2 µg/day @24 µg/kg HFA-134a 6/sex (% Change)		585.5 µg/day @71 µg/kg HFA-134a 8/sex (% Change)	
	♂	♀	♂	♀	♂	♀
Organs Weights						
Heart						
%Absolute	---	---	---	[1 16]	[1 21]	[1 27]
%Organ/Body Wt.	---	---	---	[1 6]	[1 14]	[1 20]
Lung						
%Absolute	1 17	1 15	1 17	1 16	1 32	1 26
%Organ/Body Wt.	1 13	1 10	1 5	1 6	1 26	1 19
Thymus						
%Absolute	1 38	1 59	1 60	1 83	1 85	1 87
%Organ/Body Wt.	1 35	1 58	1 55	1 81	1 83	1 86
Adrenals						
%Absolute	1 40	1 35	1 47	1 39	1 47	1 50
%Organ/Body Wt.	1 37	1 31	1 40	1 45	1 42	1 45
Liver						
%Absolute	---	---	1 5	[1 7]	1 43	1 43
%Organ/Body Wt.	---	[1 10]	[1 20]	[1 21]	1 57	1 55
Gonads						
%Absolute	---	1 19	[1 17]	1 34	[1 17]	1 34
%Organ/Body Wt.	---	1 14	1 6	1 26	1 6	1 28
Recovery Dogs	Heart*	Spleen*	Thymus*	Adrenals*	Prostate	Testes
%Absolute	1 18	1 44	1 67	1 20	1 105	1 20
%Organ/Body Wt.	1 13	1 40	1 79	1 15	1 119	1 15

NA= data not available [data in brackets did not attain statistical significance]

*Note: Data for recovery dogs represent males and females combined (n=4) except for prostate and testes where n=2.

The data in Table 9 show that treatment of dogs with fluticasone for 13 weeks resulted in dose-dependent reductions in absolute and/or relative (organ to body weights) for: Adrenals (all doses), Thymus (all doses), Heart (Mid and High dose), Lung (all doses), and Gonads (all doses females) and increased absolute and relative weights for liver (mid and high dose). High dose recovery dogs showed reductions in absolute and relative (organ to body) weights for heart (18, and 13%, respectively combined sexes); spleen (40 and 44%, respectively combined sexes); adrenals (20 and 15%, respectively combined sexes), and testes in males (33 and 28%, respectively) and increases in relative and absolute weights for thymus (67 and 79%, respectively combined sexes) and prostate in males (105 and 119%).

-Hypertrophy of bronchial/bronchiolar epithelium (min)	0	0	0	0	4	3	4	3
-↓ goblet cells in bronchial/bronchiolar mucosa	0	0	0	0	4	3	4	3
Bronchopneumonia	0	0	0	1	2	2	1	1
Pneumonia	0	0	0	0	0	0	1	1
Pneumonitis (min)	0	2	1	2	1	1	1	2
Bronchiolar Fibrosis	0	0	0	0	1	0	0	1
Bronchiolar Epithelium replaced with low cuboidal epithelium	0	0	0	0	1	0	0	1
Inflammatory exudate in Bronchi/Bronchioles	0	1	1	0	1	1	3	3
Heart								
Dilated congested vessels in A/V valve	0	0	0	0	0	0	1	0
Pathological Effects Common to Corticosteroids								
Thymus (Atrophy, minimal-marked)	0	0	1	1	3	3	4	4
Lymphnodes:								
Lymphoid depletion in paracortex								
Cervical (min-moderate)	0	0	0	0	1	0	2	3
Mesenteric (min-moderate)	0	0	0	0	1	2	2	2
Tracheobronchial (min-mod.)	0	0	0	0	1	0	1	0
↓ cellularity in medullary chords								
Cervical	0	0	0	0	0	0	2	1
Mesenteric	0	0	0	0	0	0	1	0
↓ cellularity in Cortex								
Tracheobronchial	0	0	0	0	0	0	2	0
Spleen								
Reduced White Pulp (min-marked)	0	0	0	0	0	0	4	4
Liver (Hepatocyte Rarefaction)								
Generalized (Min-moderate)	0	0	0	0	1	1	3	4
Centrilobular (min-moderate)	0	0	0	0	1	1	1	0
Adrenal atrophy;								
Zona.fasciculata/reticularis (min-marked)	0	0	3	4	4	4	4	4

NA= data not available NOAEL= ~10 µg/kg

Briefly the treatment-related histological findings were consistent with those expected following administration of corticosteroids, namely atrophy of the thymus (all doses), Lymphoid depletion in the lymph nodes (mid and high dose) with reduced cellularity in the medulla and increased cellularity in the cortex (mid and or high dose), reduced white pulp in the spleen (high dose), hepatocyte rarefaction (mid and high dose), and adrenal atrophy at (all dose groups). Other histological findings not previously observed in studies using the CFC P11/P12 propellant included **diffuse epithelial hypertrophy and hyperplasia** of the carina in mid and high dose dogs and **hypertrophy of bronchial/bronchiolar epithelium in the lungs in dogs at the mid and high dose**. Finally, one high dose male sacrificed at the end of the 13-week treatment period also showed dilated congested vessels in the atrioventricular valve, although alone, the toxicological significance of this finding appears doubtful, it is mentioned since the same effect was observed in two high dose dogs (1/sex) sacrificed at the end of the recovery period. Other histological effects detected in dogs which underwent the 4-week recovery period included: minimal lymphoid depletion in the mesenteric and/or the tracheobronchial lymph nodes on both males and one of the 2 recovery females; minimal atrophy of the zonae fasciculata/reticularis of

one of the 2 males and bronchiolar fibrosis in the lungs of two dogs (1/sex) at the high dose. Recovery dogs showed no histological correlates to the changes in weights for spleen or thymus.

Serum corticosterone and Plasma Fluticasone Levels: Tables 11 and 12 (below) present a tabulated summary of plasma fluticasone levels and mean cortisol levels prior to and after challenge with Synacthen, respectively.

Table 11. Plasma Fluticasone Levels on Week 1, 3, 6, and 13 of Treatment after Dosing with Fluticasone formulated with the HFA or the CFC propellants.

Week	Fluticasone Plasma Levels in Dogs			
	~10 µg/kg HFA Range (pg/ml)	~24 µg/kg HFA Range (pg/ml)	~71 µg/kg HFA Cmax (pg/ml)	~77 µg/kg CFC Cmax (pg/ml)
1	<50-67	<50-133	443-1124	870-1077
3	<50-132	<50-173	562-1179	554-821
6	58-173	53-152	562-1464	558-917
13	<50-168	<50-132	383-1172	322-770

The data in Table 11 above show that fluticasone was absorbed into the systemic circulation and following administration of all dose levels with increasing concentrations achieved with increasing doses. In addition, no sex related differences in plasma concentrations were observed and the exposure achieved using the HFA and the CFC formulations were comparable, with no apparent differences in the absorption between the two formulations. Inexplicable, measurable concentrations of Fluticasone propionate were observed in control animals in weeks 3 and 6 of the study. Control group fluticasone levels were: Week 1 < 50 pg/ml; Week 3: <50-89 pg/ml; Week 6: <50-130 pg/ml; and Week 13: <50 pg/ml. The Sponsor suggested in a teleconference held on July 18 that these could have been attributable to problems associated with the immunoassay used.

Table 12. Group Mean Cortisol levels (mcg/ml) in dogs measured at week 3

GR106642X		Cortisol (mcg/ml)	
		♂	♀
0.00 Vehicle Control	Prior to Synacthen	1.7	1.7
	1.5 hr post Synacthen	10.9	11.4
78.1 (µg/Day) HFA 6/sex ~10 µg/kg	Prior to Synacthen	0.5	0.5
	1.5 hr post Synacthen	5.3	5.7
195.2 (µg/Day) HFA 6/sex ~24 µg/kg	Prior to Synacthen	<0.4	<0.4
	1.5 hr post Synacthen	2.8	2.8
585.5 (µg/Day) HFA 8/sex ~71 µg/kg	Prior to Synacthen	<0.3	<0.3
	1.5 hr post Synacthen	2.7	2.2

Basal cortisol levels were dose dependently suppressed by increasing fluticasone doses. By the end of the study response to Synacthen was only slight at low dose and eliminated at intermediate and high doses. Levels in table 12 were measured during week 3 in order to

demonstrate the dose-dependent nature of the suppression. After 4 weeks of recovery reduced Synacthen response was still evident at the high dose, suggestive of adrenal hypofunction.

In conclusion, dogs administered Fluticasone propionate + GR106642X (HFA formulation) via inhalation exhibited toxicological effects consistent with the anticipated response to corticosteroids in general and similar to those observed in a previous 6 and 12 month inhalation toxicity studies in rats performed with the fluticasone/CFC P11/P12 propellant formulation. Target organs of toxicity were the adrenal (reduced weights, atrophy and hypofunction), thymus (reduced weights and atrophy); spleen (depletion of splenic white pulp), liver (increased liver enzymes, liver weights and swelling/cytoplasmic rarefaction of hepatocytes) and lymph nodes (lymphocyte depletion and/or altered cellularity of the cervical, mesenteric, and tracheobronchial lymph nodes). Cortisol levels (basal and Synacthen stimulated) were dose-dependently inhibited in all groups treated with the fluticasone/HFA formulation. Findings observed herein which have not been previously identified included diffuse epithelial hypertrophy and hyperplasia of the carina in mid and high dose dogs and hypertrophy of bronchial/bronchiolar epithelium in the lungs in dogs at the mid and high dose. The nature of these changes is unknown. Pathological findings were generally reversible at the end of the 4-week recovery period, with the exception of minimal lymphoid depletion in the lymph nodes and minimal atrophy of the adrenals which still persisted in some high dose dogs. Finally, plasma levels of fluticasone, and reductions in body weights were comparable whether fluticasone was formulated with the HFA-134A or CFC (P11/P12) propellant. Direct comparisons between fluticasone formulated with the HFA vs the CFC propellant in terms of the toxicological effects or effects on cortisol levels were not conducted. The 10 mcg/kg low dose could be considered the NOAEL for the study.

Segment II

L-706,631: Oral Segment II Teratology Study in Rats. (Report No. WPT/93/602, Vol. 11)

Study Number: R13984

Testing Lab: Glaxo Group Research Ltd, England

Study Dates: June 10, 1993 through November 8, 1994

Test Article: CC118781 in GR106642X (alternative propellant), Batch No U92/026A
GR106642X (alternative propellant), Batch No. U92/052A

Study Animals: Female AHA Rats (Wistar/Sprague Dawley derived with Wistar characteristics), 9 weeks old; 192-285 g

GLP: A statement of compliance with GLP regulations was provided.

Methods: This Segment II inhalation toxicology study was conducted in order to examine the effects of Fluticasone and the alternative propellant (GR106642X) on pregnant AHA rats and their offspring in utero. Pregnant Rats (24/group) were administered CC118781 (Fluticasone Propionate) via the inhalation route, using a snout only inhalation system, at concentrations of 0.445 (for 20 min each dose), 0.686, and 1.817 mcg/L (for 1 hour each dose). Not considering

deposition factors, estimated daily doses were: 5.5, 25.7 and 68.7 mcg/kg/day during days 7-16 of gestation. Estimated doses were calculated using the following formula:

$$\text{Dose to animal (mg/kg/day)} = \frac{\text{RMV} \times \text{T} \times \text{C}}{\text{BW} \times 1000}$$

Where T = Time of exposure (min/day); C = Chamber concentration ($\mu\text{g/L}$); BW = Body Weight (g); and $\text{RMV} = 4.19 \times \text{BW}^{0.66}$ = Respired minute volume.

An additional four mated females/group were likewise treated and used to demonstrate absorption of the test material. Finally, two other groups were administered either air (Air control) or GR106642X alone (vehicle propellant control).

Formulation: CCI18781 (Fluticasone Propionate) was formulated in GR106642X (alternative propellant).

Dose selection: Doses used were comparable to those used in the 3-month inhalation toxicity study in rats (WPT/94/028).

The following parameters were determined:

Clinical Signs of toxicity and Mortality: Daily, before and after the treatment period.

Body weights: GD 1 (day of mating), 4, 7-16, 18 and 20.

Food consumption: GD 1 (day of mating), 4, 7, 10, 13, 16, 18, and 20

Plasma levels: Not determined.

Necropsy: All females were sacrificed on GD 21, with routine post mortem examinations and examinations of major tissues and organs conducted. Uterine examinations were conducted and the pregnancy status, numbers of corpora lutea, location and number of implantations, numbers of live and dead fetuses, and early or late embryonic/foetal deaths were determined.

F1 Examinations: All Fetuses were weighed and examined externally. One half of the fetuses underwent visceral examinations were stained and under went skeletal examinations. The remaining half were fixed and underwent visceral examinations.

Results

Fluticasone inhalation in females at doses 25.7 and 68.7 mcg/kg/day during days 7-16 of gestation, produced dose-related suppression of body weight gains (24 and 47%, respectively) whereas weight gains following the cessation of dosing (Day 16 through Day 20) were comparable in all groups. High dose females also showed 9% reductions in food consumption during the treatment period, with no effects observed in other treated groups. No treatment-related deaths or abortions, or gross lesions were observed at necropsy in any of the doses tested. Table 13 (below) provides a tabulated summary of maternal and fetal observations at the Cesarean Section on GD 21.

Table 13. Maternal and Fetal Observations in Rats at Cesarean Section

Treatment	GR106642X	(Fluticasone Propionate + GR106642X)
-----------	-----------	--------------------------------------

Dose (mcg/kg)	0	5.5	25.7	68.7
Females mated	24	24	24	24
Pregnant (%pregnant)	23 (96%)	23 (96%)	22 (92%)	23 (96%)
Total Embryonic loss	0	0	1	0
Died	0	0	0	0
Corpora Lutea ¹	15.5	16.5	16.4	17.3
No. Implantation sites ¹	14.7	14.8	15.3	15.2
Preimplantation loss	5.6	7.4	6.9	12.5
Resorptions ¹	15	14	23	12
Postimplantation loss \pm SD	3.3	5.6	8.6	4.6
Total live fetuses	326	321	307	333
Mean per Female	14.2	14.0	14.0	14.5
% male live fetuses	52.8	50.8	50.2	50.8
Mean litter weights				
Mean Foetal weights	50.6 3.6	52.1 3.6	48.1 3.4	50.8 3.4

Preimplantation loss (No. Corpora Lutea - No. Implants) / No. Corpora Lutea) x 100

Postimplantation loss (No. Implants - No. Viable Fetuses) / No. Implants) x 100

¹ Values indicate the Mean value per litter

The data in Table 13 above showed no statistically significant treatment-related effects on maternal or fetal parameters with the possible exception of slight reductions (6%) in mean fetal body weights at the mid and high doses .

Tables 14 and 15 (succeeding pages) show a tabulated summary of the incidence of external, visceral and skeletal malformations and variations observed in the F1 generation..

Fetal Evaluations:

Table 14. Summary of the Incidence of Fetal External and Visceral Malformations and Variations in Rats

Dose groups (mcg/kg)	Air Control GR106642X		CCI18781 + GR106642X		
	0	0	5.5	25.7	68.7
No. Litters	21	23	22	22	23
Number of Fetuses	302	326	321	307	333

No. of Fetuses (No. of litters)

Visceral Malformations:

Major Defects

-Subclavian artery

Absent 1(1) 0(0) 0(0) 1(1) 0(0)

Abnormal origin

(retrooesophageal)	0(0)	0(0)	1(1)	0(0)	2(1)
-Innominate artery					
Absent	0(0)	1(1)	1(1)	4(2)	1(1)
Minor Defects					
-Kidney					
Pelvic cavitation					
Total incidence	14	20	36	15	15
Bilateral slight	9(6)	5(4)	13(9)	0(0)	5(2)
Bilateral moderate	1(1)	0(0)	0(0)	0(0)	0(0)
Unilateral slight	10(8)	15(10)	22(10)	14(9)	7(6)
Unilateral moderate	3(3)	0(0)	0(0)	1(1)	2(2)
Unilateral severe	0(0)	0(0)	1(1)	0(0)	1(1)
-Umbilical Artery					
Left sided	14(11)	8(5)	8(7)	18(12)	21(11)

Note: Variations which occurred at comparable or greater incidence in control groups or which occurred only at the low or mid dose were not included.

The data in table 14 show major defects (absence and or abnormal origins) in the subclavian and innominate arteries occurred at a low incidence in control and treated groups with no apparent relationship to dosing. There was a statistically significant increased incidence in the number of fetuses, but not litters, which showed the minor defect of left sided umbilical arteries (6.3% of the fetuses) which was outside the background mean range (1.3 to 5.6%). However, considering the variability of the incidence between the two control groups, and the nearness of this finding to the background range, the relationship of this finding to treatment is considered equivocal.

Table 15. Summary of the Incidence of Fetal Skeletal Malformations and Variations in Rats

	Air Control	GR106642X	CCI18781 +		
GR106642X					
Dose groups (mcg/kg)	0	0	5.5	25.7	68.7
No. Litters	21	23	22	22	23
Number of Fetuses	156	167	168	160	171
Minor Defects	No. of Fetuses (No. of litters)				
-Nasal Bone					
Incomplete ossification	6(5)	7(5)	1(1)	10(5)	12(7)
-Occipital Ossification					
Butterfly shaped	0(0)	0(0)	0(0)	0(0)	3(1)
Bipartite	0(0)	0(0)	0(0)	0(0)	2(2)
-Sternebra Ossification					
2nd Sternebra					
Incomplete ossification	16(11)	11(9)	20(11)	22(13)	24(15)
5th Sternebra					
Incomplete ossification	12(8)	17(12)	29(14)	29(17)	25(14)
6th Sternebra					
Incomplete ossification	81(21)	64(19)	87(20)	96(21)	96(20)

-Paw ossification

Metacarpals					
Incomplete ossification	60(20)	57(18)	76(19)	79(21)	87(23)
5th Metatarsals					
Incomplete ossification	2(2)	1(1)	1(1)	5(4)	7(7)

The data in Table 15 above show that administration of Fluticasone propionate formulated with the GR106642X propellant at the mid and high dose produced delayed skeletal development as was evidenced by retarded ossification in nasal bone, occipital bone, 2nd and 5th Sternebra, metacarpals of the forepaws and 5th metatarsals of the hind leg. Other changes appeared sporadically with no apparent relationship to treatment.

In conclusion, administration of fluticasone propionate (formulated with the GR106642X propellant) at doses of 5.5, 25.7, and 68.7 mcg/kg to pregnant rats produced dose-dependent reductions in body weights and delayed skeletal development in the F1 offspring at the mid and high doses. These findings are similar to those reported previously following s.c. administration of fluticasone (100 mcg/kg) to rats. The 5.5 mcg/kg dose was the no effect dose with regard to the developmental delays in ossification seen in rats.

SUMMARY AND EVALUATION:

Fluticasone Propionate/GR106642X Inhalation Aerosol is an inhaled Corticosteroid containing HFA-134A (GR106642X), intended to replace the approved drug product Flovent® (Fluticasone Propionate) Inhalation Aerosol (110 mcg and 220 mcg) which uses the CFC propellant 11/12. Flovent® formulated with the P11/P12 CFC Propellant is currently approved for the maintenance treatment of asthma as prophylactic therapy for patients 12-years of age and older. In addition a complete preclinical toxicity program for the propellant GR106642X (1,1,1,2-tetra fluoroethane, HFA-134A —) has been conducted and reviewed by the Division (See Pharmacology Review for DMF by Satish Tripathi dated 8/07/96).

Currently the Sponsor proposes to conduct a 16-week phase II comparative trial of Fluticasone Propionate (440 mcg BID or 880 mg BID versus Placebo administered via metered dose inhaler in propellant 11/12 or GR106642X clinical trial, in order to establish comparability for the two formulations. In support of the current application 3-month inhalation toxicity bridging studies with the GR106642X (HFA-134A) propellant in rats and dogs and a Segment II teratology inhalation study in rats were submitted. In addition, a 1 year inhalation toxicity study in juvenile dogs (Previously reviewed by Dr. Lawrence Sancilio in a pharmacology review for NDA 20-270 dated June 5, 1997) and mouse micronucleus tests (oral and subcutaneous) with Fluticasone (Previously reviewed by Dr. Lawrence F. Sancilio in a pharmacology review of IND 44,090 Dated February 14, 1995) were available.

In the repeated 3-month inhalation toxicity studies in rats, CCI18781 (fluticasone propionate) formulated in the HFA-134A propellant was tested at estimated doses of 0 (HFA propellant alone), 5.4, 18.2, and 84.1 µg/kg, and in the CFC P11/P12 propellant at a dose of 77.1 µg/kg (used only for plasma fluticasone and corticosterone levels; Note: estimated doses don't consider the deposition factor and overestimate the actual doses retained). The observed toxicity of the Fluticasone/HFA formulation in rats was consistent with that expected with corticosteroid treatment and observed previously in rats treated with fluticasone in the CFC formulation. Data from satellite absorption groups, which included a fluticasone/CFC P11/12 formulation group, showed comparable effects in terms of fluticasone plasma levels, inhibition of plasma corticosterone levels, and suppression of body weight gains at comparable Fluticasone formulated with the HFA-134A propellant versus that formulation and Fluticasone/CFC formulation groups.

In the 13-week toxicity study in dogs, CCI18781(fluticasone propionate) formulated in the HFA-134A propellant was tested at estimated doses of 0 (HFA propellant alone), 7.8, 19.5, and 58.6 g/kg, and in the CFC P11/P12 at a dose of 62.8 g/kg (used only for plasma fluticasone levels). In general, the observed toxicities were consistent with the toxicity profile of Fluticasone observed in previous 6-month and 12 month toxicity testing in dogs. However, in addition to the expected toxicities, dogs also showed a dose-dependent increased incidence of diffuse epithelial hypertrophy of the carina and in the lungs, hypertrophy of the bronchial/ bronchiolar epithelium and reduced number of goblet cells. Although these latter effects were shown to be reversible upon cessation of treatment, such dose-dependent effects were not documented in previous reviews of 6- and 12-month toxicity studies in dogs using the Fluticasone/CFC formulation. Finally, the current study demonstrated that comparable doses of fluticasone, formulated with either the CFC or the HFA propellant, resulted in comparable plasma and Cmax levels and suppression of body weight gains in dogs, suggesting that systemic exposure was similar between the two formulations. The 7.8 g/kg dose was the NOAEL in regard to the unexpected respiratory toxicities in dogs.

Review of the previously submitted 1-year toxicity study conducted in juvenile dogs with fluticasone propionate formulated with the HFA-134a propellant, revealed effects consistent with corticosteroid therapy and some evidence of pulmonary toxicity (See Pharmacology review by Dr. Lawrence Sancilio for NDA 20-270 dated June 5, 1997). The pulmonary effects observed in the 3-month inhalation study with Fluticasone/HFA in adult dogs (reviewed herein) were similar to those seen in the previously in the 1-year inhalation study in juvenile dogs (using the same formulation) and did not appear to progress in severity with the increased duration (1-year) of treatment.

In Segment II inhalation reproductive toxicity studies carried out in pregnant rats, administration of fluticasone propionate (formulated with the GR106642X propellant) at doses of 5.5, 25.7, and 68.7 mcg/kg produced dose-dependent reductions in body weights and delayed skeletal

development in the F1 offspring at the mid and high doses. These findings are similar to those reported previously following s.c. administration of fluticasone (100 mcg/kg) to rats. The 5.5 mcg/kg dose was the no effect dose with regard to the developmental delays in ossification seen in rats.

Previously submitted in vivo micronuclei tests conducted in mice, indicated that fluticasone propionate administered by s.c. or p.o. routes were regarded as negative for clastogenic activity. (See Pharmacology review by Dr. Lawrence F. Sancilio of IND 44,090 Dated Feb.14, 1995).

In conclusion, current 3 month inhalation toxicity studies in rats and dogs with Fluticasone formulated with the HFA-134A propellant produced toxicity profiles in each species which were consistent with the expected effects of corticosteroids in general and fluticasone in particular (based on comparisons with previously conducted studies which used fluticasone formulated with the P11/P12 CFC propellant). However, in dogs, fluticasone formulated with the HFA-134A propellant produced additional toxic effects on the respiratory tract which were not documented in previous studies using the fluticasone CFC formulation. The NOAEL in dogs was 7.8 g/kg, which may not provide a sufficient safety margin for the doses currently proposed in the 16-week clinical study.

Discussions concerning the additional respiratory effects in dogs took place between members of the Division and the Sponsor on July 18 and again on July 19. During these discussions the Sponsor proposed that the observed effects were secondary to opportunistic infections in the dog which resulted from the immunosuppressive effects of fluticasone. At the end of the discussions on July 19, the Division decided to allow the proposed 16-week clinical study to proceed based on the reversibility of the findings in dogs following cessation of dosing and the lack of progression of the pulmonary toxicity in a previously submitted 12-month inhalation toxicity study in juvenile dogs which also used the HFA-134A propellant formulation (See review by Lawrence F. Sancilio in pharmacology review of NDA 22-770 dated June 5, 1997).

In addition, the Sponsor agreed to prepare a package in support of their contention that the observed respiratory effects in the dog were related to the immunosuppressive effects of fluticasone (See minutes of July 19, 1997 telecommunication with Sponsor). And that the issue would have to be resolved prior to extension of clinical trials beyond the 16-week duration of the currently proposed clinical study and NDA approval.

Recommendations:

- 1. The Proposed clinical study should be allowed to proceed as planned.**
- 2. The Sponsor should prepare a package to address the observed respiratory toxicity in dogs prior to extension of clinical trials beyond the 16-week duration of the currently proposed clinical study and NDA approval as is shown in the draft letter to the sponsor.**

IND No. 53,502
Page 44

Shannon P. Williams, Ph.D.
Pharmacologist

cc:
Orig. IND
HFD-570/Division File
HFD-570/Williams
HFD-570/Meyer, MO
HFD-570/Barnes, CSO
N:\IND53502\pharm\97-06-18.REV

Draft Letter to Sponsor:

We have reviewed your IND application dated June 18, 1997. At this time we have the following recommendation as was conveyed in our previous telephone conversations on July 19, 1997:

Please prepare a package to address the observed respiratory toxicity in dogs prior to extension of clinical trials beyond the 16-week duration of the currently proposed clinical study and NDA approval.

Div file

AUG 5 1998

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Review #2

KEY WORDS: Inhalation toxicology, respiratory tract, 3-month study

Reviewer Name: W. Mark Vogel, Ph.D.

Division Name: Division of Pulmonary Drug Products

HFD#: HFD-570

Review Completion Date: 05 August, 1998

Electronic File Number: not applicable, entered into DFS

IND Number: 53,502

Serial Number: N 006

Submission Date: 18 AUG 1997

Submission Type: Response to request for information

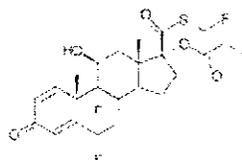
Information to Sponsor: Yes (), No (✓)

Sponsor or Agent: GlaxoWellcome

Drug: *Generic Name:* Fluticasone propionate - HFA-134a propellant

Molecular Weight: 500.6

Structure:

**Content of Submission**

In response to teleconferences on July 17, and 18, 1997, the sponsor submitted a tabulation of lung histopathology findings for each individual animal from the dog 3-month inhalation toxicity study (report WPT-92424) plus historical background data on the incidence of respiratory tract epithelial hypertrophy and hyperplasia from air or lactose control groups from five other recent dog inhalation toxicity studies. The submission also contains a proposed protocol for a 3-month study in dogs that includes a direct comparison between CFC and HFA preparations.

Relevant INDs/NDAs/DMFs:

IND 28,636 Fluticasone propionate aqueous nasal spray

IND 44,090 Fluticasone propionate multidose inhaler

IND 40,142 Fluticasone propionate Rotadisk

IND 59,703 Fluticasone propionate / salmeterol dry powder combination

NDA 20-538 Flovent inhalation aerosol

NDA 20-549 Fluticasone propionate Rotadisk inhalation powder

NDA - 20-770 Fluticasone propionate Rotadisk inhalation powder--Pediatric application

DMF: _____

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IND 53,502

Page 2

Drug Class: Glucocorticoid steroid

Indication: Asthma (12 years of age and older)

Clinical Formulation (and components): Fluticasone propionate 220 µg/actuation plus HFA134a propellant, no additional inactive ingredients.

Route of Administration: Oral Inhalation

Proposed Clinical Studies: A 16-week study (FLTA3022) at 440 or 880 µg BID is ongoing. A 6-month safety study (FLTA3021) is on hold pending an explanation for respiratory tract epithelial hyperplasia and hypertrophy found in the 3-month dog study.

Previous Reviews, Dates and Reviewers:

No. Submission:	Submission Date:	Reviewer:	Review Date:
1 Original IND	06/18/97	S. Williams	09/12/97

Studies Reviewed within this Submission: There are no new studies in this submission.

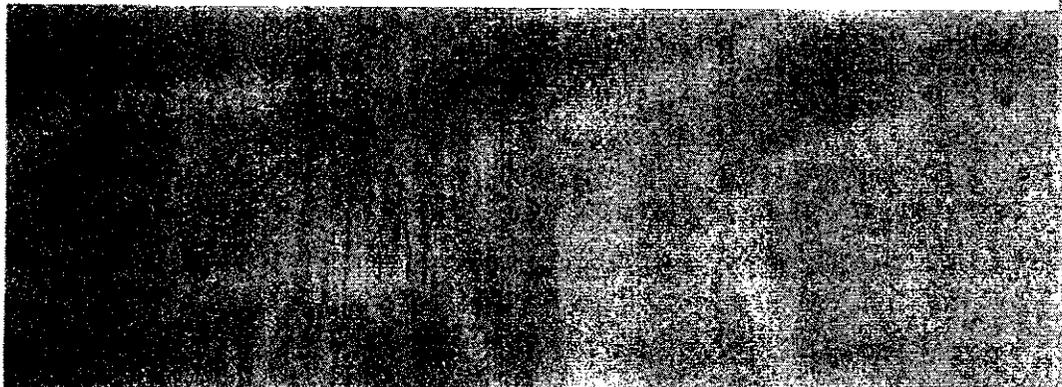
Studies Not Reviewed within this Submission: Not applicable

Studies Previously Reviewed: Not applicable

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

Introduction/Drug History: Fluticasone propionate has been approved previously in CFC aerosol and dry powder formulations for treatment of asthma. The present IND is for a new formulation using HFA-134a as the propellant. A 3-month dog study submitted in the original IND found dose related increases of epithelial hyperplasia and hypertrophy in the respiratory tract. These findings had not been noted in previous dog inhalation studies with the CFC formulation. These findings in the 3-month study were reversible, and similar findings were not increased in severity in a previous 1-year study of the HFA formulation in young dogs. For these reasons a 16-week clinical study of the HFA formulation was allowed to proceed but the sponsor was asked not to initiate a proposed 6-month study until there was an explanation for the findings. The sponsor contends that the present findings were not reported in previous studies with the CFC formulation because current inhalation studies examine and report respiratory tract histology in much greater detail than in studies conducted before the early 1990's. The sponsor interprets the observed lesions as an exacerbation of a background effect associated with opportunistic respiratory tract infection in immunocompromised dogs. The data compilation, from previous studies, is intended to document the sponsor's interpretation of the histopathological findings.

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Most of the dogs with epithelial hypertrophy in the carina also had pneumonia (7/11) as did most of the dogs with epithelial hypertrophy in the bronchi (8/14). There were a small number of dogs with pneumonia but without epithelial hypertrophy and a somewhat larger number of dogs with hypertrophy but without pneumonia. The preferential distribution of epithelial hyperplasia in animals with pneumonia was statistically significant for both the carina and the bronchi ($p = 0.006$ for both by reviewer's Fisher's exact test). These results support the sponsor's contention that respiratory tract infection is associated with hypertrophy and hyperplasia of respiratory tract epithelium.

Table 2. Association of Epithelial Findings with Pneumonia in Treated Dogs

	Carina - epithelial hypertrophy / hyperplasia	
	(-)	(+)
pneumonia or bronchopneumonia (-)	22	4
pneumonia or bronchopneumonia (+)	3	7
	Lung - bronchial epithelial hypertrophy	
	(-)	(+)
pneumonia or bronchopneumonia (-)	20	6
pneumonia or bronchopneumonia (+)	2	8

Historical Incidence of Respiratory Epithelial Hyperplasia: The background incidence of respiratory tract epithelial hyperplasia in air and lactose vehicle control dogs from five different studies initiated between 1994 and 1996 is summarized in table 3, below. There was a sporadic incidence of these findings with an overall incidence of 26% (0-50%) in the carina and 11% (0-33%) in the bronchi. This supports the sponsor's contention that hyperplasia of the respiratory tract is a background finding that may be aggravated by corticosteroid treatment.

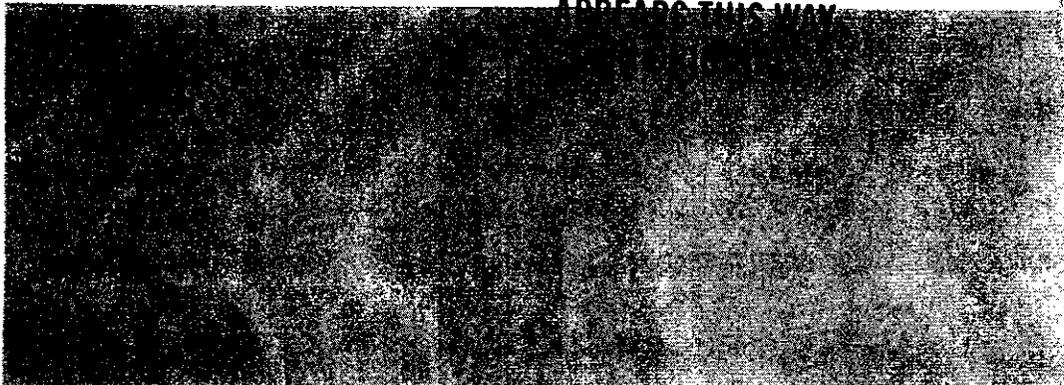
Table 3. Background Incidence of Epithelial Hyperplasia in Dog Inhalation Studies

Study Number	D14110	D20802	D20044	D20199	D20511
	5-weeks	13-wks	26-weeks	52-wks	52-weeks
Study initiation date	8/94	3/95	7/95	2/94	10/96
Treatment	air lactose	lactose	air lactose	air	air lactose
Carina/ tracheal bifurcation					
Trace		1/8		4/24	3/8 3/8
Minimal	2/6		1/8 0/8	4/24	1/8
Moderate		1/6			
Bronchial/bronchiolar					
Trace					0/8 1/8
Minimal	2/6 2/6	1/8	0/8 1/8	1/24	

Values are for males and females combined.

Overall incidence of carina/tracheal bifurcation epithelial hyperplasia = 26% (0-50%).

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Overall incidence of bronchial/bronchiolar epithelial hyperplasia = 11% (0-33%).

Re-evaluation of Fluticasone / Salmeterol Dry Powder Study: In addition to the data summaries submitted by the sponsor, a previous 13-week dog inhalation study from the same sponsor for a dry powder formulation of fluticasone was re-evaluated for the incidence of pneumonia and epithelial hypertrophy or hyperplasia. This study is number D20802 (report WPT/95/233) submitted 24 MAY 96 in original IND 50,703 for the fluticasone-salmeterol dry powder combination (reviewed by W.M. Vogel 18 OCT 96). An increased incidence of non-specific gross lung lesions and microscopic pneumonitis in treated groups was noted in the original review of that study. The study included groups treated with vehicle, fluticasone, and salmeterol alone, or with combined fluticasone and salmeterol. Because the incidence of pneumonia and epithelial hyperplasia were sporadic, the findings were not noted in the original review. However, combining bronchopneumonia and pneumonia, combining bronchial and bronchiolar hypertrophy or hyperplasia, and combining all fluticasone treated groups, a similar pattern was found as in the fluticasone HFA dog inhalation study. That is, there was an increased incidence of pneumonia and an increased incidence of respiratory epithelial hyperplasia and hypertrophy in the fluticasone treated groups. The data are summarized in table 4, below.

Table 4. Histopathological Findings in Study D20802 (Dry Powder Formulation)

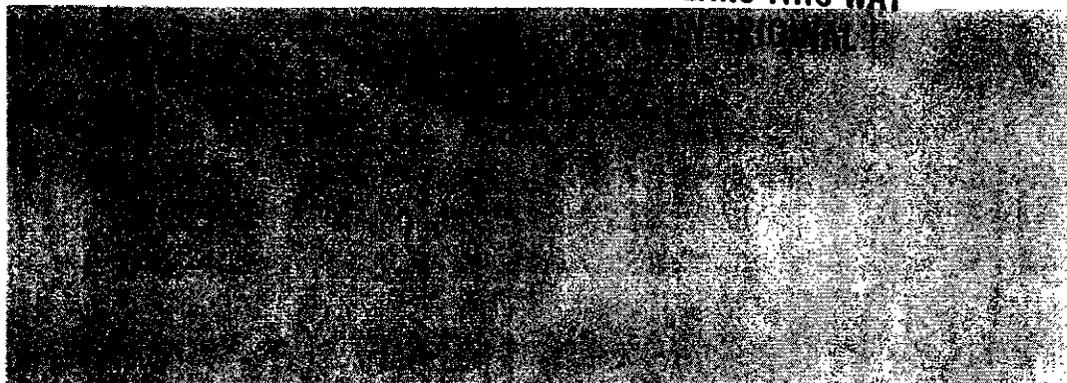
treatment n dose (µg/kg)	Control 8 0	SAL 8 15	FP/SAL 23 30/(0, 3, 15)
pneumonia or bronchopneumonia	12.5%	12.5%	30.4%
epithelial hyperplasia at tracheal bifurcation	12.5%	25.0%	26.1%
lung - bronchial/bronchiolar epithelial hypertrophy or hyperplasia	0%	0%	22%

FP = fluticasone propionate; SAL = salmeterol. Three separate groups received 30 µg/kg FP, alone or with 3 µg/kg SAL or with 15 µg/kg SAL.

Published Data: Greaves' reference on toxicological pathology¹ was consulted for further information on the association between respiratory tract infection and epithelial hyperplasia. These findings were associated with respiratory tract infection in rodents and dogs. The author notes that infection of LEW strain rats with *Mycoplasma pulmonis*, an important intercurrent respiratory pathogen in rodents, resulted in inflammation and hyperplasia of the epithelium. With infection of rats or mice by Sendai virus (para-influenza type 1) hyperplastic and multinucleated syncytial epithelial cells develop in the hyperplastic terminal bronchiolar epithelium. A similar evolution of histological changes occurred in young beagle dogs experimentally inoculated with canine adenovirus type 2.

¹ P. Greaves: *Histopathology of Preclinical Toxicity Studies*. Elsevier, New York, 1990, pp 200-203

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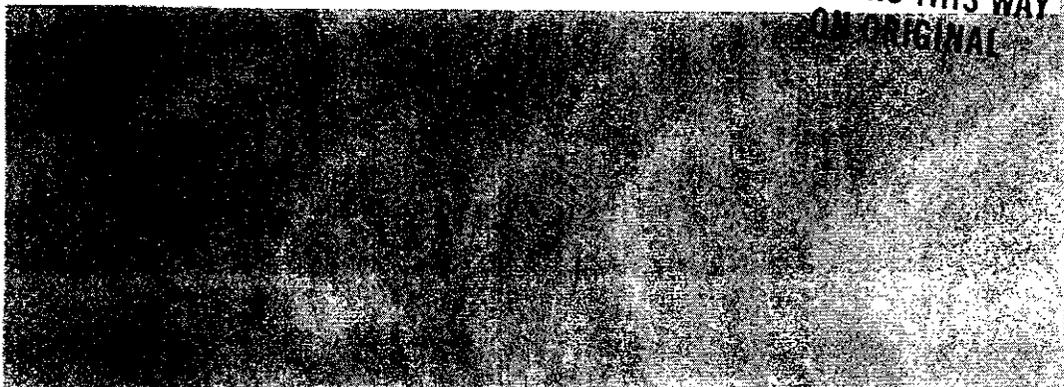
Ongoing 3-month Dog Study: In the submission of 18 August 1997 (N006), the sponsor included a draft protocol for a 3-month study directly comparing fluticasone CFC and HFA formulations in dogs. In a telephone conversation the sponsor informed us that the in life portion of the study is completed and the final study report is anticipated in summer of 1998. Male beagle dogs were allotted to the following treatment groups.

Group	Treatment	Fluticasone Dose	Number of Animals
1	Air control	0	4 + 2 recoveries
2	HFA 134a control	0	4
3	CFC 11/12 control	0	4
4	Low dose fluticasone HFA	4 x 50 µg daily	4
5	High dose fluticasone HFA	30 x 50 µg daily	4 + 2 recoveries
6	Low dose fluticasone CFC	4 x 50 µg daily	4
7	High dose fluticasone CFC	30 x 50 µg daily	4 + 2 recoveries

The low and high doses in the new study are the same as those in the previous 3-month dog study. Conventional endpoints including clinical chemistry, ophthalmoscopy, and plasma drug levels are included. Histological examination concentrates on the respiratory tract and selected target tissues (liver, spleen, heart, kidneys, thymus, adrenals, lymph nodes, gonads). This is a well designed study that should identify any toxicologically significant differences between the HFA and CFC formulations of fluticasone.

Summary: An evaluation of the data submitted by the sponsor and a re-evaluation of the data from the previous dry powder inhalation study submitted to IND 50,73 suggest that the sponsor's interpretation of lung histology findings are plausible. Hyperplasia of respiratory tract epithelium at the tracheal bifurcation (carina), in bronchi, and in bronchioles is a low incidence background finding in dogs treated as air controls or with lactose vehicle. There was a clear association between the incidence of microscopic signs of pneumonia or bronchopneumonia and the incidence of epithelial hypertrophy or hyperplasia. Not all of the dogs with epithelial hypertrophy or hyperplasia had pneumonia or bronchopneumonia. From these summary reports and reviews it is not clear exactly what microscopic changes constituted a finding of pneumonia or bronchopneumonia. It is possible that the dogs with epithelial hypertrophy or hyperplasia, but without pneumonia or bronchopneumonia, had other manifestations of infection. In fact, all but one of the dogs with epithelial hypertrophy or hyperplasia, but without pneumonia or bronchopneumonia, had a finding of inflammatory exudate in the bronchi or bronchioles, which would also be consistent with respiratory tract infection. Experimental respiratory tract infection in rodents and dogs has been associated with epithelial hyperplasia. Finally, increased incidences epithelial hyperplasia/hypertrophy were observed with the dry powder fluticasone formulation, in conjunction with increased incidence of pneumonia and bronchopneumonia when the findings were combined and

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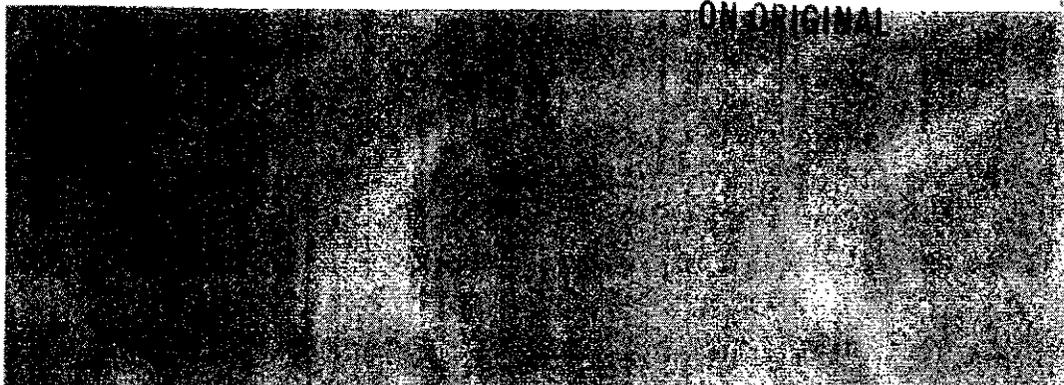
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Group	Treatment	Fluticasone Dose	Number of Animals
1	Air control	0	4 + 2 recoveries
2	HFA134a control	0	4
3	CFC 11/12 control	0	4
4	Low dose fluticasone HFA	4 x 50 µg daily	4
5	High dose fluticasone HFA	30 x 50 µg daily	4 + 2 recoveries
6	Low dose fluticasone CFC	4 x 50 µg daily	4
7	High dose fluticasone CFC	30 x 50 µg daily	4 + 2 recoveries

The low and high doses in the new study are the same as those in the previous 3-month dog study. Conventional endpoints including clinical chemistry, ophthalmoscopy, and plasma drug levels are included. Histological examination concentrates on the respiratory tract and selected target tissues (liver, spleen, heart, kidneys, thymus, adrenals, lymph nodes, gonads). This is a well designed study that should identify any toxicologically significant differences between the HFA and CFC formulations of fluticasone.

Summary: An evaluation of the data submitted by the sponsor and a re-evaluation of the data from the previous dry powder inhalation study submitted to IND 50,73 suggest that the sponsor's interpretation of lung histology findings are plausible. Hyperplasia of respiratory tract epithelium at the tracheal bifurcation (carina), in bronchi, and in bronchioles is a low incidence background finding in dogs treated as air controls or with lactose vehicle. There was a clear association between the incidence of microscopic signs of pneumonia or bronchopneumonia and the incidence of epithelial hypertrophy or hyperplasia. Not all of the dogs with epithelial hypertrophy or hyperplasia had pneumonia or bronchopneumonia. From these summary reports and reviews it is not clear exactly what microscopic changes constituted a finding of pneumonia or bronchopneumonia. It is possible that the dogs with epithelial hypertrophy or hyperplasia, but without pneumonia or bronchopneumonia, had other manifestations of infection. In fact, all but one of the dogs with epithelial hypertrophy or hyperplasia, but without pneumonia or bronchopneumonia, had a finding of inflammatory exudate in the bronchi or bronchioles, which would also be consistent with respiratory tract infection. Experimental respiratory tract infection in rodents and dogs has been associated with epithelial hyperplasia. Finally, increased incidences epithelial hyperplasia/hypertrophy were observed with the dry powder fluticasone formulation, in conjunction with increased incidence of pneumonia and bronchopneumonia when the findings were combined and

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IND 53,502

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steroid-treated groups pooled. All of these results are consistent with the sponsor's interpretation that the increased incidence of respiratory epithelial hypertrophy and hyperplasia were a secondary effect related to immunosuppression and resultant respiratory tract infection. The occurrence of increased respiratory epithelial hypertrophy and hyperplasia in dogs treated with the dry powder formulation indicates that this finding is not unique to the new HFA formulation. Nonetheless, the results of sponsor's ongoing dog inhalation study of fluticasone HFA and CFC formulations will provide additional useful information with direct, head to head comparison of two formulations under the same conditions.

In a telephone conversation initiated by the Division, the sponsor informed us that they anticipate submitting the data from the ongoing 3-month dog study (directly comparing CFC vs HFA formulations) in late summer before initiating the 6-month clinical study later this fall. Therefore, there is no need to contact the sponsor until the results of the 3-month dog study have been submitted and reviewed.

RECOMMENDATIONS

1. An analysis of available data suggests that epithelial hypertrophy seen in dogs exposed to fluticasone in an HFA formulation: 1) has a low incidence in untreated controls from other studies; 2) was also increased by fluticasone dry powder in dogs; and 3) is correlated with histologic evidence of pneumonia/bronchopneumonia and may be secondary to immunosuppression.
2. The sponsor does not plan to initiate the 6 month clinical trial of HFA fluticasone until after results of the 3-month dog study comparing HFA and CFC fluticasone formulations have been submitted. Therefore, further regulatory action regarding this issue is not necessary pending submission and review of the 3-month dog study.

Original IND 53,502
c.c. HFD-570/Division File
HFD-570/S. Barnes
HFD-570/R. Meyer
HFD-570/C.J. Sun
HFD-570/W.M. Vogel

W. Mark Vogel 05 August 1998
Mark Vogel, Ph.D., Pharmacologist

Cheryl Johnson Aug 5, 1998

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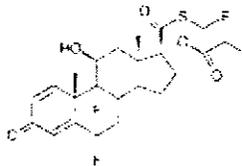
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Review #3

KEY WORDS: Inhalation toxicology, respiratory tract, 3-month study
Reviewer Name: W. Mark Vogel, Ph.D.
Division Name: Division of Pulmonary Drug Products
HFD#: HFD-570
Review Completion Date: 00 November, 1998
Electronic File Number: not applicable, entered into DFS
IND Number: 53,502
Serial Number: N 031
Submission Date: 21 August, 1998
Submission Type: Response to request for information
Information to Sponsor: Yes (✓), No ()
Sponsor or Agent: GlaxoWellcome

Drug: *Generic Name.* Fluticasone propionate - HFA-134a propellant
Molecular Weight. 500.6

Structure:



Content of Submission:

A 3-month study in dogs with a direct comparison between CFC and HFA fluticasone formulations.

Relevant INDs/NDAs/DMFs:

- IND 28,636 Fluticasone propionate aqueous nasal spray
- IND 44,090 Fluticasone propionate multidose inhaler
- IND 40,142 Fluticasone propionate Rotadisk
- IND 59,703, Fluticasone propionate : salmeterol dry powder combination
- NDA 20-548 Flovent inhalation aerosol
- NDA 20-549 Fluticasone propionate Rotadisk inhalation powder
- NDA - 20-770 Fluticasone propionate Rotadisk inhalation powder-Pediatric application
- DMF # _____

Drug Class: Glucocorticoid steroid

Indication: Asthma (12 years of age and older)

Clinical Formulation (and components): Fluticasone propionate 220 µg actuation plus HFA134a propellant, no additional inactive ingredients.

Route of Administration: Oral Inhalation

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IND 53,502

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Proposed Clinical Studies: A 6 month safety study (FLTA3021) has recently been initiated.

Previous Reviews, Dates and Reviewers:

No. Submission	Submission Date:	Reviewer:	Review Date:
1 Original IND	06/18/97	S. Williams	09/12/97
2 Summary of epithelial hypertrophy findings from previous studies.	08/18/97	W. M. Vogel	08/05/98

Studies Reviewed within this Submission: Report WD1998 00282/00, CC118781 (in P11/P12 or GR1106642X): 13 weeks inhalation toxicity study in the beagle dog (Study Number D21998), report dated 31 July 1998.

Studies Not Reviewed within this Submission: None
Studies Previously Reviewed: None

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

Introduction/Drug History: Fluticasone propionate has been approved in CFC aerosol and dry powder formulations for treatment of asthma. The present IND is for a formulation using HFA-134a as the propellant. A 3-month dog study submitted in the original IND found dose related increases of epithelial hyperplasia and hypertrophy in the respiratory tract. These findings had not been noted in previous dog inhalation studies with the CFC formulation. These findings in the 3-month study were reversible, and similar findings were not increased in severity in a previous 1-year study of the HFA formulation in young dogs. For these reasons a 16-week clinical study of the HFA formulation was allowed to proceed but the sponsor was asked not to initiate a proposed 6-month study until there was an explanation for the findings. The sponsor contends that the present findings were not reported in previous studies with the CFC formulation because current inhalation studies examine and report respiratory tract histology in much greater detail than in studies conducted before the early 1990's. The sponsor interprets the observed lesions as an exacerbation of a background effect associated with opportunistic respiratory tract infection in immunocompromised dogs. A data compilation, from previous studies was submitted 08/18/97 (N006) to document the sponsor's interpretation of the histopathological findings. The review of that submission concluded that epithelial hypertrophy in dogs exposed to the HFA fluticasone formulation: 1) has a low incidence in untreated controls from other studies; 2) was also increased by fluticasone dry powder in dogs; and 3) is correlated with histologic evidence of pneumonia bronchopneumonia and may be secondary to immunosuppression.

In the submission of 08/18/97 the sponsor also indicated that they were planning a direct comparison of CFC vs HFA fluticasone formulations in dogs. The present submission reports the results of that 13-week dog study.

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REVIEW OF TOXICOLOGY

CC118781 (in P11/P12 or GR106642X): 13 weeks inhalation toxicity study in the beagle dog (Study Number D21998). Report WD1998-00282.00, vol 6.1, page 125

Study Dates: Experimental 12/11/97 to 03/12/98, report issued 07/31/98

Testing Lab:

Test Articles: Fluticasone propionate in CFC11/CFC12 propellant, batch W0307MA

Fluticasone propionate in HFA 134a propellant, batch 7ZX003B

CFC11/CFC12 propellant control, batch 197/212B

HFA 134a propellant control, batch 7ZX005A

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

QA Report: Yes (✓) No ()

Methods: Male beagle dogs (5.5-8 months old, 6.4-11.8 kg) were randomized to the following treatments:

Group	Treatment	Fluticasone Dose		No. of Animals
		Nominal	Delivered µg/kg	
1	Air control	0	0	4 - 2 recoveries
2	HFA134a control	30 × 0 µg daily	0	4
3	CFC 11/12 control	30 × 0 µg daily	0	4
4	Low dose fluticasone HFA	4 × 50 µg daily	8	4
5	High dose fluticasone HFA	30 × 50 µg daily	77	4 - 2 recoveries
6	Low dose fluticasone CFC	4 × 50 µg daily	7	4
7	High dose fluticasone CFC	30 × 50 µg daily	64	4 - 2 recoveries

The low and high doses in the new study are the same as those in the previous 3-month dog study with HFA fluticasone. Drug was administered, twice daily, by metered dose inhalers connected to an oropharyngeal tube. Vehicle-treated dogs received the same number of actuations per day as the high dose groups. The delivered dose was calculated by subtracting the amount deposited on the dosing apparatus from the amount released from the MDI. Aerosol particle size was determined by cascade impactor. Two animals each from the air control and high dose fluticasone groups were allowed a 4-week recovery period after the 13-week dosing period. The following observations were made:

Clinical signs at least twice daily

Body weight weekly

Food intake measured daily, calculated weekly

Ophthalmology prestudy and weeks 4 and 13

Clinical pathology prestudy and weeks 5, 13, and recovery

Plasma cortisol prestudy, day 8, weeks 5, 13, and recovery

Plasma drug levels day 1, weeks 3, 6, 9, and 13 at -5, 10, 20, 40, 120, and 240 min post-dose.

Necropsy terminal

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Histopathology: a comprehensive list of tissues was saved and fixed; only the following target tissues were examined: adrenals, heart, kidney, larynx, liver, lung, lymph nodes (retropharyngeal, mesenteric, medial tracheobronchial, cervical) nasal cavity, oro-naso pharynx, spleen, thymus, trachea (with carina), gross lesions.

Results: (summarized in Table 1, page 5)

Mortality: None

Clinical Signs: Transient "nodding of the head" occurred sporadically to frequently in 3 high dose CFC fluticasone dogs, one high dose HFA fluticasone dog (on only one occasion), and in 2 CFC vehicle dogs. This appears to be a reaction to the propellant, which was more marked with CFC than HFA propellant.

Body Weight: No toxicologically significant treatment-related effects.

Food Intake: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Hematology: Sporadic statistically significant differences among groups did not appear to be treatment related.

Clinical Chemistry: Plasma glucose was decreased slightly in the high-dose fluticasone CFC group (12%↓). Plasma creatinine was decreased in HFA (17%↓) and CFC (21%↓) high-dose fluticasone groups (statistically significant only for the CFC fluticasone group). Baseline and ACH-stimulated plasma cortisol levels were decreased in both HFA and CFC high-dose fluticasone groups, more so in the CFC fluticasone group.

Organ Weights: Adrenal weight was decreased in both HFA and CFC high dose fluticasone groups reaching statistical significance only in the CFC fluticasone group. Adrenal weight did not fully recover during 4 weeks off treatment. Thymus and spleen weights were not decreased significantly.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Systemic effects included increases in the incidence and severity of adrenal atrophy and thymus involution in fluticasone treated groups. As with adrenal weight, microscopic evidence of atrophy was still evident after the recovery period. Local airway effects included increased incidence of bronchitis in the lungs and tracheal bifurcation (carina). Respiratory epithelial hypertrophy and hyperplasia, and pneumonia or bronchopneumonia observed in previous studies were not noted in the present study.

Toxicokinetics: Plasma levels, as measured by AUC, were quite variable from week to week. However, exposure clearly increased with increasing dose. Plasma levels were higher after the second daily exposure than after the first. Average systemic exposure was comparable for the HFA and CFC formulations, systemic exposure tended to be greater with the HFA formulation than with the CFC formulation at the low dose but not

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IND 53,500

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at the high dose.

Table 1. Findings in 13-Week Dog Inhalation Toxicity Study

	Controls			Fluticasone			
	Air	HFA	CFC	HFA		CFC	
				Low	High	Low	High
Delivered dose (µg/kg)	0	0	0	8	77	—	64
Particle size MMAD (µm)	---	---	---	2.88		2.68	
% of particles < 3 µm	---	---	---	54		59	
AUC₀₋₂₄ (pg-hr/mL)							
1st inhalation day 1				148	150	16	455
2nd inhalation day 1				377	395	110	1042
1st inhalation week 3				73	597	10	597
1st inhalation week 6				266	971	78	430
1st inhalation week 9				437	769	161	608
1st inhalation week 13				193	595	66	798
2nd inhalation week 13				136	712	273	1275
Avg 1st inhalation wks 1-13				223	616	66	560
Avg. C_{max} 1st inhalation wks 1-13 (µg/mL)							
[range]				80 (0-353)	205 (0-715)	14 (0-217)	236 (37-573)
Nodding of the head	0/6	0/4	2/4	0/4	1/6	0/4	2/6
Glucose (mM) wk 13	5.51	5.72	5.5	5.49	5.68	5.66	4.84
Creatinine (µM) wk 13	72	70	69	69	60	70	57
Cortisol (ng/mL) wk 13							
Basal	31	14	20	12	11	27	1.5
ACTH stimulation	139	121	142	104	37	128	4.3
Adrenal weight (g) wk 13							
recovery	1.20	1.14	1.38	1.12	1.03	1.26	0.72
	1.53	—	—	—	0.92	—	0.86
Histopathology							
Adrenal atrophy 13 wk							
recovery	0/4	0/4	0/4	2/4	4/4	2/4	4/4
	0	—	—	—	1/2	—	2/2
Lung bronchioles							
minimal	0	0	0	1	3	0	0
slight	0	0	0	1	1	1	3
Carina bronchus							
slight	0	1	0	0	2	1	3
moderate	0	0	0	0	0	0	1
Tonsillitis							
	2/4	2/4	2/4	2/4	4/4	1/4	3/4
Thymus involution							
slight	0	0	1	2	0	2	0
moderate	0	0	0	0	2	0	4

Highlighted cells indicate p<0.05 vs air control.

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SUMMARY AND EVALUATION

Systemic Effects: Systemic effects identified in this study are expected consequences of glucocorticoid administration, principally adrenal and lymphoid atrophy. Lymphoid atrophy was evident only as histological changes in the thymus, spleen, and lymph nodes were not measurably affected in this study. Decreased plasma creatinine and glucose are also expected glucocorticoid effects, reflecting alterations of protein and carbohydrate metabolism. Adrenal suppression was manifested as decreased organ weight, decreased basal and ACTH-stimulated plasma cortisol, and microscopic changes. Adrenal changes at the high dose did not completely recover during 4 weeks off treatment. The systemic effects were dose related. Systemic effects were more marked in the CFC-fluticasone group. But, considering the small number of animals and the marked day to day variability in systemic exposure, it is not clear that this represents a real difference between formulations. In any event, there is clearly no evidence of increased systemic activity with the new HFA formulation. The only unexpected effect was "head nodding" that occurred in 2 CFC vehicle dogs, 3 high dose CFC fluticasone dogs, and 1 high dose HFA fluticasone dog. This appears to be a reaction to the propellant, which was more marked with CFC than HFA propellant.

Systemic glucocorticoid effects in the present study were less marked than in the original 3-month dog inhalation study, in which spleen, liver, lymph nodes, and gonads were additional targets, along with further changes in hematology and clinical chemistry. The extent of plasma cortisol suppression was also more marked in the previous study. Nominal delivered high dose was the same in both studies (~70 µg/kg); but peak plasma levels of fluticasone were higher in the previous study (ranges of 1-2 µg/mL for HFA and 2-4 µg/mL for CFC in the original study vs 0.5-1 µg/mL for HFA and 1-2 µg/mL for CFC in the present study). Differences in inhalation technique between the two different laboratories conducting the studies may account for the substantial difference in systemic exposure at similar nominal doses.

Respiratory Tract Effects: This study was designed as a follow-up study to characterize the increased incidence of respiratory epithelial hyperplasia and hypertrophy observed with the HFA formulation in the original 3-month inhalation toxicity study. (There was no direct comparison of histology between HFA and CFC formulations in the previous study.) The specific findings of epithelial hyperplasia and hypertrophy were not observed in the present study. One possible explanation for the absence of the finding in the present study might be relatively less drug deposition in the respiratory tract in the present study due to differences in inhalation technique. That would be consistent with the lower systemic exposure observed in the present study compared to the original study. The sponsor's data analysis submitted 8/18/97 indicated that the findings were usually observed in the presence of pneumonia or bronchopneumonia. The latter findings were also not observed in the present study. Lack of pneumonia and bronchopneumonia would also be consistent with a lower deposited dose in the present study and reinforces the

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sponsor's interpretation that respiratory epithelial hyperplasia and hypertrophy are associated with pneumonia and bronchopneumonia. Another factor that could contribute to the absence of respiratory epithelial hyperplasia and hypertrophy in the present study is that the finding had only sporadic occurrence in previous studies. For example, the increased incidence in steroid-treated groups was only evident with the dry powder fluticasone salmeterol formulation when several steroid-treated groups were pooled (see Pharm-Tox review of IND 53,502 by W. M. Vogel dated 08-05-98).

Although respiratory epithelial hyperplasia and hypertrophy were not observed in the present study, fluticasone-treated groups in the present study had increased incidence of "bronchitis" in lung and at the tracheal bifurcation. The report indicates that "bronchitis" consisted principally of minimal or mild, diffuse, neutrophil infiltration of the bronchial epithelium which was in some cases accompanied by single cell necrosis and minimal hypercellularity of the bronchial epithelium. It is possible that these findings represent a milder form of the pneumonia and bronchopneumonia observed in previous studies. The incidence of bronchitis in the present study was dose-related with no obvious difference between the HFA and CFC formulations.

Conclusion: In a direct comparison of HFA and CFC formulations of fluticasone propionate in a 13-week dog inhalation toxicity study there was no measurable difference in systemic exposure between formulations with slightly greater systemic effects observed for the CFC formulation. Local respiratory tract effects consisted of a dose-related increase in the incidence of bronchitis in the lung and tracheal bifurcation (carina) with no difference between formulations. This study provides satisfactory bridging to the previous CFC formulation and indicates that the systemic and local respiratory tract toxicity profiles of the two formulations are comparable.

RECOMMENDATIONS

This study indicates that the systemic and local respiratory tract toxicity profiles of the CFC and HFA fluticasone formulations are comparable. Along with the sponsor's previous data reanalysis, this study alleviates concern that the HFA formulation might be causing local airway effects not observed with the CFC formulation. The preclinical data support the sponsor's proposed phase-3 clinical studies and no additional preclinical studies are needed in support of the HFA formulation.

IND 53,502

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Draft Letter to Sponsor:

We have reviewed your submission of August 21, 1998 (13-week inhalation toxicity study of HFA and CFC fluticasone propionate formulations in dogs). Along with the preclinical data analysis submitted August 18, 1997, these data would support your proposed clinical development program.

W. Mark Vogel 10/21/98
Mark Vogel, Ph.D., Pharmacologist

Original IND 53,502
c.c. HFD-570 Division File
HFD-570/S. Barnes
HFD-570/C.J. Sun
HFD-570/W.M. Vogel

Cheryl [unclear] Nov 6 1998

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DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
 REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
 NDA 20-770, Review No. 1

NDA: 20-770

Serial Number: 1

Date of Submission: 9/26/96

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

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Review Completed: 6/2/97

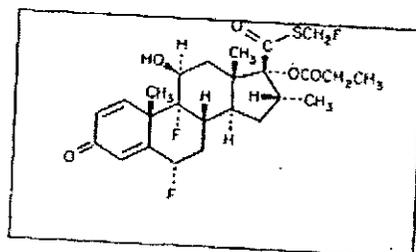
Sponsor: Glaxo Inc.
 5 Moore Drive
 Research Triangle Park, NC 27709

Drug Name: Fluticasone propionate

Chemical Name: 5-fluoromethyl 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrost-1,4-diene-17 β -carbothioate

CAS No. 80474-14-2

Structure:



Molecular Weight and Formula: 500.6 (C₂₅H₂₁F₃O₅S)

Related NDAs, NDAs: IND 28,636, NDA 20-121 (nasal spray)
 IND 29,039 (oral inhaler)

NDA 20-770

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IND 40,142

Class: Glucocorticoid

Indication:

Clinical Formulations: Micronized fluticasone propionate, 50-100 mcg/dose
Lactose q.s. to 25 mg

Route of Administration and Dose: Inhalation aerosol; 50-100 µg twice daily.

Previous Review(s), Date(s), and Reviewer(s):

NDA 20-121, Nasal Spray, A. Mukherjee, 3/29/93.

NDA 20-121, Nasal Spray, B. Hayes, 5/3/94

NDA 20-549, Rotodisk Inhalation, L.F. Sancilio, 12/13/95

Preclinical Studies Submitted and Reviewed in this NDA

Fluticasone propionate has been approved for use as a nasal spray, a metered dose inhaler and an inhalation powder. Its pharmacology and toxicology has been reviewed which is amended to this review. A 1-year inhalation study in juvenile dogs was submitted in this NDA. This was undertaken to determine whether the steroid administered by inhalation would affect the maturation of the respiratory tract since this NDA is for the use of inhaled fluticasone propionate in young patients 4 to 11 years of age. No other preclinical studies are warranted for the approval of this NDA.

Toxicology

Multi-Dose

52-Week Inhalation Study in Juvenile Dogs, No. WPT/95/096, Vol. 1.2, p 9.

GLP signed statement: Yes.

Site the study was conducted:

Study Dates: 2/16/94- 1/31/96

Study Report Date: 2/16/96

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Method

Animals: Nine-10 week old M and F (2.3-5.3 kg) Beagle dogs, (12 M and 12 F/
group)

Housing: 4/ kennel from 0 to week 5; thereafter 2 of the same sex and dose group were
housed in each kennel.

Compounds: Fluticasone propionate (Batch No. U93/057A), GR106642X, HFA Propellant,
(Batch No. U93/262A 510)

Formulation: Aerosol in a MDI containing fluticasone propionate and the propellant,
GR106642X or the propellant alone. Administration was by inhalation via an oropharyngeal
tube. The total dose delivered was 74 (65-82) mg for each metered dose. Each metered dose
contained 50 µg of fluticasone propionate. Mass median aerodynamic diameter (MMAD) ±
geometric standard deviation: —

Dose: Group 1, Control (Sham)

Group 2, Propellant, Weeks 1-8, 30 metered doses/day; Weeks 9-52, 15 metered
doses/day

Group 3, Fluticasone propionate, Week 1, M, 126 and F, 140 µg/kg/day;

Week 8, M, 82 and F, 91 µg/kg/day;

Weeks 8-52, M, 25 and F, 26 µg/kg/day

Due to adverse effects, the dose was reduced at week 8 and thereafter. The initial dose was
selected from a 4-week toxicity study in juvenile dogs whereby an inhalation dose of 508
µg/dog was tolerated.

The following parameters were determined.

Clinical Observations: Daily.

Body Weight: Prior to start of study and weekly thereafter.

Food Consumption: Weekly; results are expressed as mean daily food consumed per dog.

Ophthalmoscopy: Prior to start of study and during weeks 4, 12, 25 and 51.

Electrocardiography: Prior to start of study and during weeks 4, 12, 25 and 51.

Chest Girth Measurement: Prior to start of study and during weeks 4, 12, 25 and 51.

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Abdominal Girth Measurement: Prior to start of study and during weeks 9 (1 M and 1 F in Groups 2 and 3), 12, 25 and 51.

Long Bone Measurements: Prior to start of study and during weeks 8, 12, 24, 36 and 48 of dosing and at necropsy.

Radiography of Neck: Under anesthesia lateral radiographs were taken prior to start of study and during week 52.

Physical Appearance: Photographs (full side and lateral side view) were taken during weeks 9, 12, 25 and 51 of 1 M and 1 F in Groups 2 and 3 during weeks 9, 12, 25 and 51.

Hematology, Urine Analysis, Clinical Chemistry: Prior to start of study and during weeks 8, 13, 26 and 52.

Plasma Cortisol Levels: Immediately before and 1.5 h after stimulation with Synacthen (250 µg i.v./dog.) Prior to start of study and during weeks 8, 13, 26 and 52.

Plasma Levels of fluticasone propionate:

Groups 1 and 2: Day 1, 20 min and 24 h after dosing.

Weeks 4, 8, 13, 26 and 52, before dosing, and 20 min after dosing (weeks 4 and 8) on each occasion.

Group 3: Day 1, before dosing then 5, 10, 20, and 40 min, and 2, 4 and 24 h after the first dose.

Weeks 4, 8 and 13: before dosing, and 20 min after dosing (weeks 4 and 8) on each occasion.

Weeks 26 and 52: before dosing then 2, 5, 10, 20, and 40 min, and 2, 4 h after dosing on each occasion.

Necropsy

Organs weighed were: adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes with epididymides, thymus, prostate and thyroids with parathyroids. The whole lungs were weighed, the right lobe was weighed wet and dried (48 h at 50°C).

Tracheas were measured in the following manner: 1. Total length (distance from the cricoid cartilage to the bifurcation); 2. The number of rings from the cricoid cartilage to the bifurcation; 3. The horizontal and vertical external diameters of the 2nd, 10th, 20th and 30th rings; 4. The width of the 2nd, 10th, 20th and 30th rings.

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Tissues examined histologically were: adrenals, brain, heart, kidneys, liver, spleen, thymus, larynx, tracheal bronchial lymph nodes and trachea with bifurcation. For lungs, the apical (left), cardiac (left), intermediate and both diaphragmatic lobes including the bronchus/bronchioles and peripheral lung sections.

Results

Mortality: Group 1: None.

Group 2: 1 F (week 31), sacrificed for humane reasons.

Group 3: 1 M (week 7), cause of death unknown.

Group 3: 1 F (week 8), operated for hernia and did not improve, killed for humane reasons.

Group 3: 1 F (week 9), enlarged hernia, sacrificed for humane reasons.

Group 3: 1 F (week 31), difficult hernia, sacrificed for humane reasons.

Clinical Observations: These are summarized in the following table.

Observations at 52 Weeks	Incidence		
	Group 1(Sham)	Group 2 (Vehicle)	Group 3 (Test)
Hernia			
Umbilical	0/24	1/23	13/24*
Eye Discharge	0/24	0/23	7/20
Abdominal Distension			
Slight to Marked	0/24	0/23	12/20
Hair Loss/Thinning			
Ears	2/24	0/23	20/20
Legs/Feet	1/24	1/23	16/20
Chest	0/24	0/23	5/20
Back	1/24	0/23	16/20

*Include 4 animals that were sacrificed during the 52 weeks.

Body Weight: Group 1 vs Group 2: Week 8, no effect.

Group 3 vs Group 2: Week 8, M, -19%, F, -17%

Week 52, M, -16%, F, -12%

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Food Consumption: Based on cumulative effect: Group 3 vs Group 2: Weeks 1- 8, no effect
Group 3 vs Group 2: Weeks 9-52, M, -3.2%
F, -6.7%

Ophthalmoscopy: Epiphora (abnormal outflow of tears down the cheek): Group 1, 0/24,
Group 2, 0/23, Group 3, 10/20.

Electrocardiography: No effect.

Girth Measurement: The results are summarized in the following table.

Area	% Change From Group 2 (Vehicle)	
	Group 1 (Sham)	Group 3
Abdominal		
Week 25	M, +2.5 F, +5.7	M, +6.7 F, +15.9
Week 51	M, +8.4 F, +11.0	M, +2.3 F, +12.4

Changes in the chest girth was not remarkable.

Long Bone Measurements:

Time of Measurement	% Change From Group 2 (Vehicle)	
	Group 1 (Sham)	Group 3
Week 8	M, -3.0 F, -1.0	M, -12.1 F, -14.4
Week 53	M, -2.4 F, 0	M, -10.4 F, -13.6

Radiography of Neck: No data given.

Photographs: Week 9: Majority of animals in Group 3 showed: 1. a stunted physical appearance of short tail and snout with pot belly abdomen, and 2. protruding/enlarged eyes.

Hematology and Clinical Chemistry changes are listed in the following table.

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Parameter	% Change From Group 2 (Vehicle) by Group 3			
	Week 8		Week 52	
	M	F	M	F
White Blood Count	13*	41	25*	3*
Neutrophils	36	88	33	12*
Lymphocytes	-41	-61	18*	-14*
Eosinophils	-100	-100	-84	-77
Monocytes	212	200	35*	133*
Partial Thromboplastin Time	27	16	19	11*
Fibrinogen	28	33	42	38
Alkaline Phosphatase	34	27	16*	40
LDH	31*	46	32	20
α HBDH (α -hydroxybutyrate dehydrogenase)	50*	75	5	16*
Serum Phosphorous	-13	-27	14	10
Cholesterol	23	27	37	43
Triglycerides	31*	41	12*	17*

* P > 0.05

Cortisol Levels in Response to Synacthen (% Decrease):

Week 8: M, Prior to administration of Synacthen: > 69%
1.5 h after administration of Synacthen: > 96%
F, Prior to administration of Synacthen: > 85%
1.5 h after administration of Synacthen: > 97%

Week 52: M, Prior to administration of Synacthen: > 82%

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1.5 h after administration of Synacthen: > 97%

F, Prior to administration of Synacthen: > 87%
1.5 h after administration of Synacthen: > 98%

Urine Analysis: Weeks 8 and 52: Increase in pH in M and F.

Plasma Levels

Fluticasone propionate was assayed in plasma using a radio immune assay. The Limit of Quantification was --- ng/ml for weeks 1 and 8 and 52, respectively. Since there was no difference in the plasma levels in the M and F dogs, the results were pooled. During the study, the plasma levels of fluticasone propionate prior to its administration were low, ranging from < --- ng/ml at weeks 1 and 8 and < --- ng/ml at week 52. The 20 and 40 min mean plasma levels are shown in the following table.

Day	Mean Plasma Level ng/ml, N=8	
	20 min	40 min
7	0.99	1.14
56	0.98	ND
182	< 0.72	0.79
364	0.78	0.78

ND, Not determined

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Necropsy

Organ Weight: The results are summarized in the following table.

Organ Weight	% Change From Group 2 (Vehicle)			
	Absolute		Relative	
	M	F	M	F
Liver	+15	+37	+27	+38
Adrenals	-56	-62	ND	ND
Thyroids	No Change	+22	ND	ND
Lungs (whole)	-30	-36	ND	-26
Left Lobe (wet)	-39	-34	ND	ND
Left Lobe (dry)	-41	-37	ND	ND
Gonads	-26	No Change	ND	ND

ND, Not Determined

Tracheal Measurements: Change From Group 2 (Vehicle) by treated (Group 3) group.

No. of Tracheal Rings: M and F, no change.

Length: M, -11.6%, F, -12.3%

The results of the tracheal ring dimensions are shown in the following table.

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Ring Location	% Decrease From Group 2 (Vehicle), p < 0.05	
	Males	Females
C2		
Horizontal External Diameter	14.1	14.6
Vertical External Diameter	14.4	16.8
Width (height)	12.5	13.1
C10		
Horizontal External Diameter	25.1	23.2
Vertical External Diameter	21.1	18.4
Width (height)	12.5	8.3
C20		
Horizontal External Diameter	28.5	26.8
Vertical External Diameter	19.3	22.9
Width (height)	10.1	18.4
C30		
Horizontal External Diameter	30.0	27.4
Vertical External Diameter	24.4	25.3
Width (height)	22.9	23.5

Macroscopic Pathology: The results are summarized in the following table. Data from the Sham-treated animals were not presented since none of the findings in the treated animals were seen in the sham-treated animals.

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Organ/Finding	Incidence			
	Males		Females	
	Control (Vehicle) N= 11	Treated 11	Control (Vehicle) 12	Treated 9
External Appearance				
Hair Thinning/Loss	0	5	0	3
Ventral abdomen, comedones	0	8	0	5
Pot-Bellied	0	6	0	8
Skin, thin and/or flaky	0	7	0	5
Inguinal hernia	0	3	0	2
Skeletal Muscle				
Abdominal wall, thin	0	6	0	3
Body Cavities				
Abdomen and thorax, Abundant adipose tissue	0	6	0	8
Lungs				
Soft pale patchy non- collapsible areas/foci	0	4	0	2
Trachea				
Mucosal Surface, mucoid Material adhering to surface	0	6	0	1
Slight distortion in orientation of rings (misshaapen trachea)	0	2	0	1
Liver				
Texture, friable	0	6	0	6
Rounded Edges	0	2	0	6
Adrenal Gland				
Thinning of cortex	0	10	0	8
Thymus				
Not visible	0	8	0	7

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Histopathology:

In the 4 (1 M and 3 F) animals that died or killed for humane reasons, pathologic changes seen that were related to treatment were marked thymus involution (2/3 F), sparse germinal centers in the tracheobronchial lymph nodes (1/1 M, 1/3 F), reduced cellularity of the white pulp of the spleen (1/1 M, 3/3 F), minimal swelling/cytoplasmic rarefaction of centrilobular hepatocytes (2/3 F) and atrophy of the zonae fasciculata and reticularis of the adrenals (1/1 M, 2/3 F). The respiratory tract showed decreased basophilia of bronchial cartilages (1/1 M, 2/3 F), alveolar septal mineralization (3/3 F), pneumonia (1/1 M, 3/3 F), hypertrophy of bronchial epithelium with decreased prominence of goblet cells, dilated bronchial glands (1/1 M, 3/3 F) and inflammatory exudate in the trachea and larynx (2/3 F). The hernia seen in the 3 F dogs was due to an apparent exacerbation of a preexisting condition resulting from the asthenia of the abdominal muscle caused by fluticasone propionate.

The results seen in animals at termination are summarized in the following table. Data from the Sham treated animals were not presented since none of the findings were seen in this group.

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Organ/Finding	Incidence			
	Males		Females	
	Control (Vehicle) N= 11	Treated 11	Control (Vehicle) 12	Treated 9
Larynx				
Inflammatory Exudate	0	6	0	1
Carina				
Focal mineralization of tracheal cartilages	2	7	1	0*
Trachea				
Area of luminal distortion and dilation	0	1	0	1
Lungs				
Decreased width and decreased basophilia of bronchial cartilages	0	10	0	9
Focal mineralization of bronchial cartilages	0	6	0	6
Mineralization of bronchial walls	0	2	0	6
Hypertrophy of bronchial/bronchiofaryngeal epithelium	0	9	0	5
Decreased prominence of goblet cells in bronchial/bronchiolar mucosa	0	6	0	3
Dilated bronchial glands	0	8	0	7

* carina from 1 animal was lost

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Organ/Finding	Incidence			
	Males		Females	
	Control (Vehicle) N= 11	Treated 11	Control (Vehicle) 12	Treated 9
Mucus and inflammatory cells in bronchi/bronchioles	2	5*	1	3*
Tracheobronchial lymph node Sparse germinal centers	3	6*	1	5
Liver				
Generalized swelling/cytoplasmic rarefaction of hepatocytes	0	6	0	4
Swelling/cytoplasmic rarefaction of centrilobular hepatocytes	0	4	0	5
Adrenals				
Atrophy of zonae fasciculata and reticularis	0	11	0	9
Spleen				
Generalized reduced cellularity Of white pulp	0	10	0	3*
Thymus				
Involution				
Total	6	8	5	7*
Marked	0	6	0	6
Pneumonia	0	3*	0	2*

* P > 0.05

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Summary and Conclusion

A 1 year inhalation study was conducted in juvenile dogs with fluticasone propionate. This study was undertaken to determine whether fluticasone propionate causes unexpected developmental changes in the respiratory tract of young animals which can be extrapolated to children for which fluticasone propionate will be used.

In M and F juvenile beagle dogs, initial doses of 126/140 $\mu\text{g}/\text{kg}$ (0.49 mg, total dose) were administered by inhalation. This dose was selected from the results of 52-week and 4-week studies in dogs. A dose of 501 $\mu\text{g}/\text{dog}$ was well tolerated in the 4-week study. In this study, after 8 weeks, the dose was reduced to 25/26 $\mu\text{g}/\text{kg}$ (0.25 mg, total dose) because of toxicity. The median MMAD was 2.1 μm indicating that deposition occurred in the tracheobronchial region.

At the end of 8 weeks, 1 M and 1 F in the treated group died. The cause of death in the M was unknown; the F that was operated for a hernia as an indirect result of fluticasone propionate administration was killed for humane reasons. The other animals showed marked weight loss, abdominal distension and eye discharge as a result of the steroid effect.

At the end of 52 weeks weight loss was still evident; clinical toxic signs were umbilical hernias, abdominal distension, excessive eye tearing and hair loss and thinning. The animals showed a stunted appearance. Food consumption was slightly decreased from week 8 to 52.

The increased incidence of umbilical hernias and pot-bellied abdomens was probably due to a preexisting condition that was exacerbated by the thinning of the abdominal wall as a consequence of the glucocorticoid effect by fluticasone propionate. Increased abdominal girth was quite evident at week 25 and not at week 51. Changes were not seen with the chest girth. Long bone lengths were decreased at week 8 and continued to be less than the control (vehicle) group by week 53. These effects were also related to the steroid effect.

Changes in the white blood count were more prevalent at 8 weeks than at 51 weeks. Neutrophils and monocytes were increased and lymphocytes were decreased. At week 52, only the eosinophil count was still markedly decreased in the M and F. Consistent changes in clinical chemistry parameters were increased fibrinogen and cholesterol levels. Urinary pH was elevated.

Adrenal suppression was quite evident indicating a full steroid effect. At week 8 and thereafter, cortisol levels were markedly low prior to and after administration of the adrenal cortex stimulant, Synacthen. This was further reflected by changes in the adrenal glands. There was a decrease in adrenal weight; macroscopically, the cortex showed thinning.

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Microscopically, there was atrophy of the zonae fasciculata and reticularis. These changes are characteristic of exogenous corticosteroid administration.

The plasma levels at 20 min following inhalation at week 8 was approximately 25% higher than that seen at 20 and 40 min on week 52. Since the dose at week 8 was > 3 times that at week 52, the change in the pharmacokinetics may be attributed to the toxic effects of fluticasone propionate.

At necropsy, there were an increase in the absolute and relative weights of the liver, and decreased absolute and relative lung weight. Changes in the liver were attributed to generalized swelling/cytoplasmic rarefaction of hepatocytes and centrilobular hepatocytes. There was a decrease in absolute wet weight and a decrease in absolute dry weight of the right cardiac lobe of the lung. The respective decrease and increase in absolute wet and dry weights as the sponsor indicated were the result of decreased secretions and increased alveolar thickness that are characteristic of glucocorticoids.

Emphasis was placed on the effect of fluticasone propionate on the development respiratory tract, in particular, the trachea. The number of tracheal rings was not affected. There was a decrease in the width, vertical and horizontal external diameters of tracheal rings C2, C10, C20 and C30. The highest change was seen at ring C30. Macroscopically, the tracheas of 3/20 dogs showed a slight distortion in orientation of rings; histologically, 2/3 (1 M and 1 F) of these animals showed an area of luminal distortion and dilation. Inflammatory exudate was present in the larynx and focal mineralization or mineralization occurred in the carina, bronchial cartilages and bronchial wall. The lungs showed decreased width and decreased basophilia of the bronchial cartilages, hypertrophy of the bronchial/bronchiolar epithelium, decreased prominence of goblet cells, the presence of mucus and inflammatory cells in the bronchi/bronchioles, dilated bronchial glands, sparse germinal centers in the tracheobronchial lymph nodes, reduced cellularity of the white pulp of the spleen and thymus involution. Some of these effects were related to the immunosuppression produced by fluticasone propionate. The pneumonia in some animals was also attributed to immunosuppression.

SUMMARY and EVALUATION

This NDA is for fluticasone propionate to be administered by inhalation as a dry powder for the prophylactic treatment of asthma in children 4-11 years old. The maximum human daily inhalation dose is 100 µg twice a day. The formulation consists of fluticasone propionate and lactose, a commonly used excipient for dry powder inhalers. The Pharmacology and Toxicology of fluticasone propionate have been studied in depth. Attached is the review of the pharmacologic and toxicologic studies submitted in NDA 20-549 for dry powder fluticasone propionate for use in adolescents and adults 12 years of age and older.

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In this NDA a 1 year inhalation study was conducted in juvenile beagle dogs 9-10 week old. Focus was on the respiratory tract to determine whether unusual changes occurred in the respiratory tract. The following tables compares the findings in the 1 year study in juvenile and adult dogs. In the adult study, the dogs received from metered dose inhalers (50 μg /burst) 4, 10 and 30 bursts in divided doses daily. This was equal to 7.8, 16.8 and 50 μg /kg in M and 7.3, 19.1 and 51.5 μg /kg in F; in the juvenile dogs only 1 dose level was tested. They received from metered dose inhalers (50 μg /burst) 30 bursts in divided doses 4 hr apart daily. Initially, the dose was 126-140 $\mu\text{g}/\text{kg}$ which after 8 weeks due to toxicity, the dose was decreased to 25-26 $\mu\text{g}/\text{kg}$ (15 bursts). Comparison was made with the 50-51.5 $\mu\text{g}/\text{kg}$ dose in adult dogs and the one dose level in juvenile dogs. Data for the adult dogs were taken from the review of Dr. Mukherjee (NDA 20-121, 3/29/93).

Although both groups received 30 bursts from the fluticasone inhaler, the dose in the juvenile dogs was higher than that in the adult dogs (weeks 1 and 9, 126/140 and 82/91 $\mu\text{g}/\text{kg}$ vs 50/51.5 $\mu\text{g}/\text{kg}$) prior to being lowered after week 8. However, the plasma levels were apparently comparable (plasma levels were determined 20 and 40 and 30 min following inhalation in the juvenile and adult dogs, respectively) throughout the study. Despite decreasing the daily inhalation dose in the juvenile dogs from 126-140 $\mu\text{g}/\text{kg}$ to 25/26 $\mu\text{g}/\text{kg}$ on week 8 due to toxicity, the plasma levels were similar throughout the study. There were no obvious reasons other than possible alteration in bioavailability to account for the similarity in plasma levels especially during the first 8 weeks whereby the inhalation dose in the juvenile dogs was approximately 3 times the dose in the adult dogs. Toxicity was not a factor since it was not evident in the juvenile animals until after week 4.

Although both groups showed signs of hypercorticosteroidism, the juvenile animals showed increased systemic toxicity thereby indicating greater sensitivity than the adult dogs, i.e., abdominal hernias, eye discharge and reduced cellularity of white pulp in the spleen. Some of the juvenile animals were moribund and were killed on a humane basis. This maybe due to different pharmacokinetics because after week 8, the inhalation dose of fluticasone propionate given to the juvenile dogs was half that administered to the adult animals (25-26 $\mu\text{g}/\text{kg}$ vs 50-51.5 $\mu\text{g}/\text{kg}$) and yet showed similar plasma levels. Respiratory tract toxicity was quite evident in the juvenile dogs; none of the pathological changes observed in the juvenile dogs were seen in the adult dogs animals. This may be a local effect since the dose in the juvenile dogs was 124-140 and 82/91 $\mu\text{g}/\text{kg}$ during the first 8 weeks in contrast to 50-51.5 $\mu\text{g}/\text{kg}$ throughout the study in the adult animals. Although the daily dose was reduced to 25-26 $\mu\text{g}/\text{kg}$ after 8 weeks in the juvenile dogs, it cannot be determined whether the respiratory changes were initiated or already induced during the first 8 weeks of dosing.

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Observation/Parameter	Present, + Absent, 0	
	Adult Beagle Dog	Juvenile Beagle Dog
	50-51.5 μ g/kg	26-140 μ g/kg to 25-26 μ g/kg
Mortality/Moribund Condition	None	C, 1/24, T, 4/24
Body Weight	M, -30%, F, +11%	M, -16%, F, -12
Abdominal Hernia	0	+
Abdominal Distension	+	+
Eye Discharge	0	+
Hair Loss/Thinning	+	+
Long Bones, \downarrow in Length	Not Determined	+
Eosinophilia	0	+
Fibrinogen Levels, \downarrow	0	+
Cholesterol Levels, \downarrow	+	+
Creatinine and Urea Levels, \downarrow	+	0
Thymus Atrophy	+	+
Liver Weight, \downarrow	+	+
Rarefication of Centrilobular Hepatocytes	+	+
Adrenals, Cortical hypoplasia	+	+
\downarrow Adrenal response to stimulation	+	+
Spleen, reduced cellularity of white pulp	0	+
Plasma level, ng/ml		
Day 1	0.92 ^c	
Day 7		0.99 ^a 1.14 ^b
Day 32	1.07	
Day 56		0.98 ^a
Day 182/185	0.88 ^c	<0.72 ^a 0.79 ^b
Day 361/364	0.78 ^c	0.78 ^a 0.78 ^b

^a Determined 20 min after dosing

^b Determined 40 min after dosing

^c Determined 30 min after dosing

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Respiratory Tract Changes	Present, + Absent, 0	
	Adult Beagle Dog 50-51.5 µg/kg	Juvenile Beagle Dog 126-140 1-25-26 µg/kg
Trachea, ↓ in Diameter of tracheal rings C2, C10, C20, C30	0	+
↓ Tracheal Length	0	+
Disorientation of rings/ Is this considered misshapen trachea (?)	0	+(3/23)
Area of luminal distortion and dilation	0	+
Larynx, Inflammatory Exudate	0	+
Carina, Focal mineralization of tracheal cartilages	0	+
Lungs, Decreased width and decreased basophilia of bronchial cartilages	0	+
Bronchi, Focal mineralization of bronchial cartilages	0	+
Mineralization of bronchial walls	0	+
Hypertrophy of bronchial/bronchiolar epithelium	0	+
Decreased prominence of goblet cells in bronchial/bronchiolar mucosa	0	+
Dilated bronchial glands	0	+
Mucus and inflammatory cells in bronchi/bronchioles	0	+
Tracheobronchial lymph node, Sparse germinal centres	0	+

Fourteen day pharmacokinetics study was conducted with inhaled fluticasone propionate in pediatric patients at the maximum daily dose of 200 µg/day. The plasma levels ranged from — pg/ml. The following table show that the plasma levels in juvenile dogs during this 1 year study were 5-41 x the plasma levels observed with the maximum daily inhalation dose in pediatric patients. Since the only dose level tested in the 1 year juvenile dog study showed toxicity, it was not possible to determine an adequate safety margin based on comparative plasma levels.

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Day	20 or 40 min Mean Plasma Level in Juvenile Dogs pg/ml, N=8	Plasma Levels in Juvenile Dogs Relative to Human Plasma Levels, 28.1-154 pg/ml, in Pediatric Patients (N=13)
7	1140	7-41
56	980	6-35
182	790	5-28
364	780	5-28

Points Discussed with Medical Officer

Information was related to the Medical Officer, Dr. M. Purucker, that fluticasone propionate in juvenile dogs at a toxic inhalation dose produced a low but not significance incidence (3/20) of disorientation of tracheal rings. This reviewer's recommendation is that the changes in the structure of the trachea in juvenile dogs by inhaled fluticasone propionate do not pose a potential clinical adverse effect.

Labeling Review

1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 ✓ § 552(b)(5) Draft Labeling

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RECOMMENDATIONS

This NDA is for fluticasone propionate to be administered by inhalation as a dry powder for the treatment of asthma. It is similar to NDA 20-549 except that fluticasone propionate will be administered to patients 4-11 years. From a preclinical standpoint, this NDA is approvable.

The proposed changes in the label for the preclinical areas are recommended.

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Lawrence F. Sancilio 6/2/97

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

Chyngophon June 5, 1997

cc. Division File, NDA 20-770
/RMeyer, HFD-570
/C.S.O., HFD-570
/LSancilio, HFD-570
/JSun, HFD-570

Attachments: NDA 20-121, A. Mukherjee, 3/29/93
NDA 20-549, L.F. Sancilio, 12/13/95

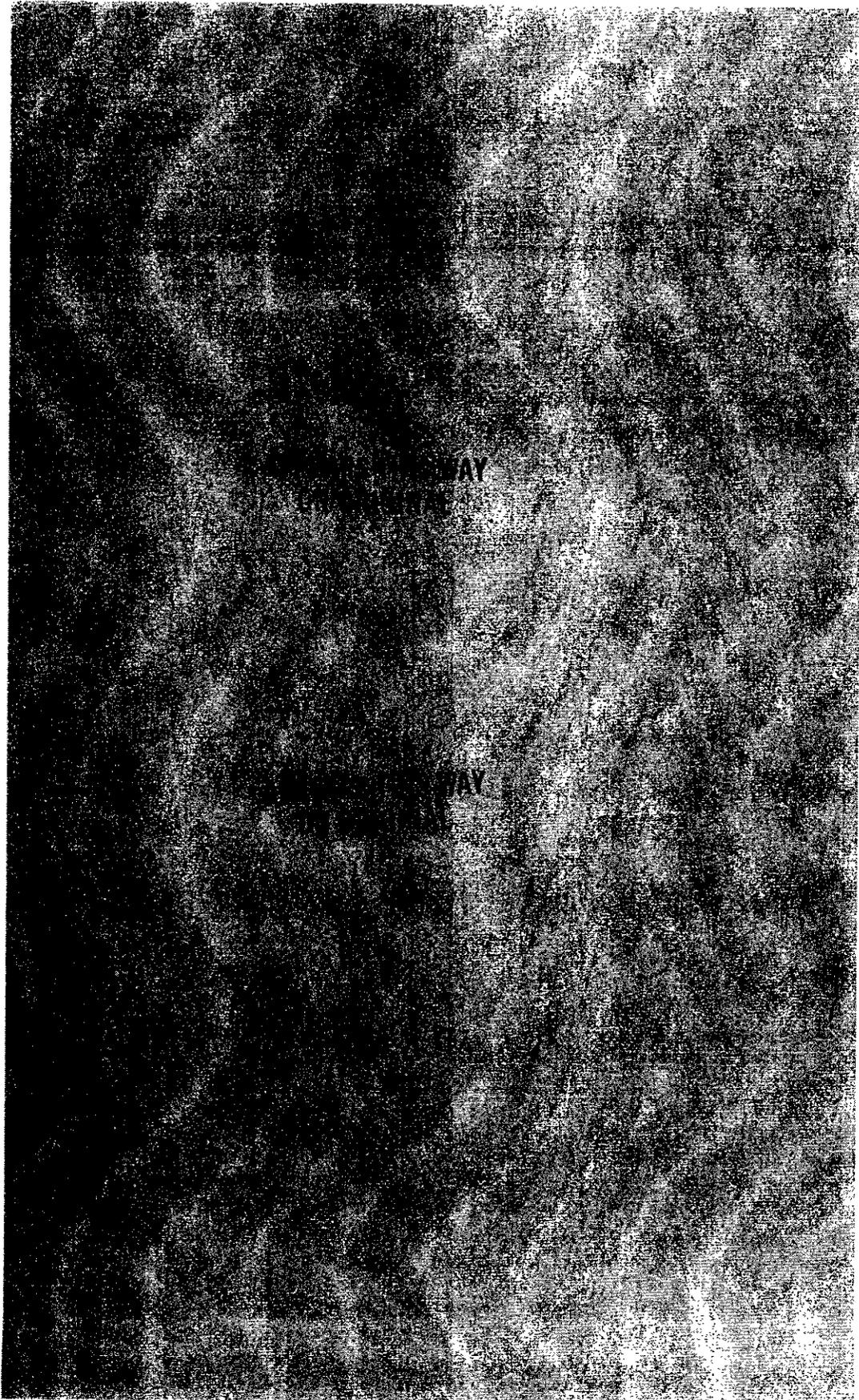
Approved by J. Sun, Ph.D.

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/s/

Lawrence Sancilio
12/20/02 03:35:55 PM
PHARMACOLOGIST

Joseph Sun
12/20/02 05:21:51 PM
PHARMACOLOGIST
I concur.