CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-833

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA
Chemistry Consult

Reviewer: Lawrence F. Sancilio, Ph.D.

Division: PULMONARY DRUG PRODUCTS, HFD-570

Reviewer Completion Date: 12/8/99

NDA No. 20-833

Date of Consult Request: 11/2/99

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

Drug: Fluticasone propionate

Trade Name: Flovent Diskus

Class: Glucocorticoid

Indication: Prophylactic treatment of asthmatic patients >4 years old.

Formulation: ——— powder with lactose. Each blister strip contains 50 100 or 250 µg in 12.5 mg of lactose. The amount of fluticasone propionate delivered per dose is 47, ——— ncg, respectively.

Route of administration: Inhalation.

Maximum Daily Dose: ———

These doses were based on the amount of fluticasone propionate delivered from each actuation.

Request:

Dr. Koble requested that the safety of the — of the inhaler be determined.

2 Page(s) Withheld

Recommendations

The following are acceptable at the concentrations proposed: _____

_____

_____ is not acceptable with the information submitted. It is recommended that the sponsor submit the _____ to enable us to determine whether _____ this compound is safe.

Letter to the Sponsor

[S] 12/8/99

Lawrence F. Sancilio, Ph.D.

cc. /Division File, NDA 20-833, HFD-570
/MPurucker, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570
/DKoble, HFD-570

[S]
acting PT team Leader.

APPEARS THIS WAY
ON ORIGINAL

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

NDA: 20-833

Date of Submission: 3/31/98

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

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Review Completed: 12/9/98

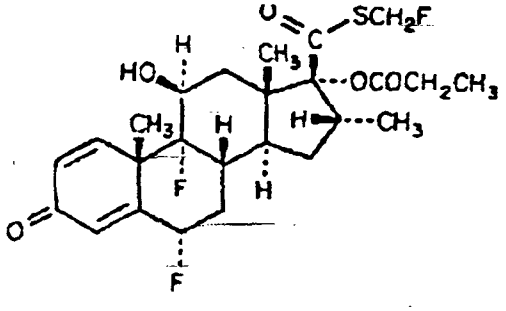
Sponsor: Glaxo Inc.
5 Moore Drive
Research Triangle Park, NC 27709

Drug Name: Fluticasone propionate. Flovent[R] Diskus

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

CAS No. 80474-14-2

Structure:



Molecular Weight and Formula: 500.6 ($C_{25}H_{21}F_3O_5S$)

Class: Glucocorticoid

Indication: Maintenance treatment of asthma as a prophylactic therapy in patients 4 years of age and older.

Formulation: There are 3 fluticasone propionate powder dosing formulations. Each contains 50 mcg, 100 mcg or 250 mcg/dose of — fluticasone propionate in a 12.5 mg of lactose. The amount of fluticasone propionate delivered per dose is 47, ——— mcg, respectively.

Route of Administration: Inahaltion.

Maximum Daily Dose

4 /

These doses were based on the amount of fluticasone propionate delivered from each actuation.

Summary and Evaluation

This NDA is for fluticasone propionate to be administered as a dry powder by inhalation for the maintenance treatment of asthma as a prophylactic therapy in patients 4 years of age and older. The same 3 dose dry powder formulations of fluticasone propionate in this NDA have already been approved for the treatment of asthma in Flovent Rotadisk (NDA 20-549 and NDA 20-770). The Pharmacology and Toxicology of fluticasone propionate have been studied in depth (see the reviews of the pharmacologic and toxicologic studies submitted in NDAs 20-121, 20-549 and 20-770).

Labeling Review

The following changes in the label regarding preclinical data are recommended. Deletions are highlighted with a ~~strikeout~~ and additions are highlighted in **Bold.** Relationship of the preclinical dose to the maximum recommended human inhalation dose based on body surface was calculated using km factors of 6 for rats, 3 for mice, 12 for rabbits, 37 for Adults and 16 for a 4 year old child.

Line 370

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults and approximately 10 times the maximum recommended daily inhalation dose in children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg ———————————————

Line 381

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg ——————————— the

maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Line 385

Pregnancy: Teratogenic Effects: Pregnancy Category C: Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively, a

Line 390

In the rabbit, fetal weight and cleft palate were observed at a subcutaneous dose of 4 mcg/kg -the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) of fluticasone propionate.

Line 397

Fluticasone propionate crossed the placenta following

Lines 407

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk.

Line 511

The oral and subcutaneous median lethal doses in mice and rats were >1000 mg/kg

RECOMMENDATIONS

This NDA is for fluticasone propionate to be administered by inhalation for the maintenance treatment of asthma as a prophylactic therapy in patients 4 years of age and older. From a preclinical standpoint, the NDA is approvable with the recommended changes in the label.

/S/ 12/9/95

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

/S/ , 1995

cc. /Division File, NDA 20-833, HFD-570
/MPurucker, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570
/JSun, HFD-570
Attachments: Reviews of NDAs 20-121, 20-549 and 20-770

APPEARS THIS WAY
ON ORIGINAL