CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-247

PHARMACOLOGY REVIEW

EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA
LABEL REVIEW

NDA No.: 21-247
Date/type of submission: 11/04/05/ Labeling amendment
Information to Sponsor: Yes (X), No ( )
Sponsor: Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Reviewer: Lawrence F. Sancilio, Ph.D.
Division: PULMONARY AND ALLERGY PRODUCTS
Reviewer Completion Date: 11/21/05
Drugs:
Trade Name: Aerospan HFA.
Generic Name: Flunisolide Hemihydrate
Code Name: Unknown.
Chemical Name: Pregna-1, 4-diene-3, 20-dione, 6-fluoro-11, 21-dihydroxy-16, 17-[(1-methylethylidene) bis (oxyl)]-hemihydrate, (6α 11β, 16α)
Drug Class: Glucocorticoid

Indication: Prophylactic and maintenance treatment of asthma in adult and children ≥ 6 years old.

Aerospan HFA is a pressurized, metered dose aerosol for oral inhalation. Each actuation delivers 80 mcg of flunisolide hemihydrate (equivalent to 78 mcg of flunisolide).

Route of Administration; Daily Dose: Inhalation; Adults (≥ 12 years old) —mcg/day and children (6-11 years old), — mcg/day.

Labeling review:

Additions are in **BOLD** and deletions are in ~~STRIKE OUT~~. The ratios of the animal dose to the maximal clinical inhalation dose in adults and children are presented in the table below.

Recommendation

From a preclinical perspective, the label is approved with the recommended changes.

Lawrence F. Sancilio, Ph.D.

Reviewer's signature: _____

Supervisor's signature:

Concurrence - _____

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/s/

Lawrence Sancilio
11/22/2005 09:35:09 AM
PHARMACOLOGIST

Joseph Sun
11/23/2005 02:33:19 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY COVER SHEET
Chemistry Consult

NDA number: 21-247
Date/type of submission: 10/04/03
Request date: 3/4/04; 3/12/04
Sponsor: Forest Laboratories, Inc.

Reviewer name: Lawrence F. Sancilio, Ph.D.
Division name: Division of Allergy and Pulmonary Drug Products
HFD: 570
Review completion date: 4/9/04

Drug: Flunisolide Hemihydrate aerosol; 60 and 120 actuations (— ug/actuation)

Drug class: Glucocorticoid

Indication: Treatment of asthma.

Route of administration: Inhalation

Response to Chemistry Consult Requested by Brian Rogers, Ph.D.

Description of the Consult

This is a request to determine whether the proposed acceptance criteria of the daily exposure of proposed leachables in the flunisolide inhalation (Aerospan) aerosol are acceptable.

Review

The inhalers for Aerospan aerosol inhalers contain 60 and 120 actuations (85 ug/actuation). The maximum daily dose of flunisolide is — ul. The total volume /container over the shelf-life are — ml for the 60 actuation inhaler and — ml for the 120 actuation inhaler. Based on — ul/actuation and the overfill, there are — daily doses in the 60 actuation inhaler and — daily doses in the 120 actuation inhaler. The daily exposure of each leachable is determined from the following formula:

$$\text{Daily exposure of leachable (ng/kg)} = \frac{\text{Proposed Acceptance Criterion}}{\text{No. of daily doses/inhaler}} \div 50\text{kg}$$

The results are summarized in the following table.

Class/Leachable	Proposed Acceptance Criterion NMT ug/can	Daily Exposure, NMT ng/kg		Acceptability	
		60 Dose Inhaler	120 Dose Inhaler	60 Dose Inhaler	120 Dose Inhaler

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Recommendations

The following table list the acceptance criteria for the — inhalation product that should be targeted for those compounds whose proposed acceptance criterion was unacceptable.

Compound	Target Acceptance Criterion for Acceptability based on safe exposure limits ug/can of
[	7
[	7
Total leachable	

[a] If technically feasible

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____

cc. BRogers
RLostritto
LJafari

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/s/

Lawrence Sancilio
4/9/04 01:36:04 PM
PHARMACOLOGIST

Joseph Sun
4/9/04 01:59:18 PM
PHARMACOLOGIST
I concur.

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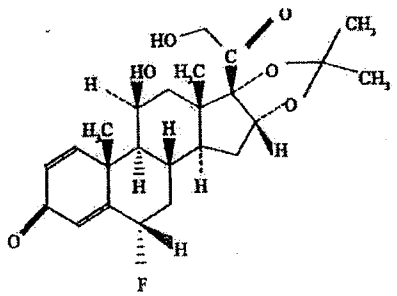
EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA

NDA No.: 21-247
Serial No./Type of Submission: Study conducted in response to FDA request.
Dates of Submission: 5/1/03
Information to Sponsor: Yes ( ), No (X)
Sponsor: Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Reviewer: Lawrence F. Sancilio, Ph.D.
Division: PULMONARY AND ALLERGY DRUG PRODUCTS
HFD: 570
Reviewer Completion Date: 5/28/03
Drugs:

Trade Name: Aerobid.
Generic Name: Flunisolide Hemihydrate
Code Name: Unknown.
Chemical Name: Pregna-1, 4-diene-3, 20-dione, 6-fluoro-11, 21-dihydroxy-16, 17-[(1-methylethylidene) bis (oxyl)]-hemihydrate, (6α 11β, 16α)
CAS Registry No.: 77326-96-6
Mole File No.: Unknown
Molecular Formula/Molecular Weight: $C_{24}H_{31}O_6H$. ½ H_2O/443.51
Structure:



. 1/2 H_2O

Relevant, NDAs and DMFs: IND ——— and 51,456, NDA 18-148 (flunisolide nasal solution) and 18-340 (flunisolide CFC MDI), and DMF ———————

Drug Class: Glucocorticoid

Indication: Prophylactic and maintenance treatment of asthma in adult and children ≥ 4 years old.

Route of Administration; Daily Dose: Inhalation; Adults (≥ 12 years old) mcg/day and children (4-11 years old), — mcg/day.

Background

In Aerospan, one of the impurities of the parent compound, ' ——— possesses a structure alert. Studies indicated that ——— was genotoxic in the CHO Chrosomal Aberration Assay. Unless qualified, the acceptance criterion should be <0.1% for both drug substance and drug product. For qualification of the genotoxicity, the sponsor was recommended to test ——— in the sensitive SHE Cell Assay to show that it was not potentially carcinogenic, or to test it in the P-53 Assay or in the 2-year rodent Carcinogenicity Assay to show that it was not carcinogenic. In the March 31, 2003 telecon, the sponsor indicated that ——— ——— was inactive in the SHE Cell Assay. This assay was submitted for review in this submission.

Review

Study Title: In vitro transformation of Syrian Hamster Embryo (SHE) cells by 7-day exposure with ———

Key Findings: ——— was inactive in the SHE Cell Assay.

Study No.:23463-0-485R
Vol. No. and Page No.: 1, 1.
Conducting Laboratory and Location: ———
Date of Study Initiation: 1/15/03.
GLP Compliance: Yes.
QA Reports: Yes (X); No ( ).
Drug, Lot No.; % Purity: RD0672/82; 96.4-96.9%.
Formulation/Vehicle: ———

Methods

Strains/species/cell line: Embryo cells derived from ime pregnant Syrian Golden hamsters at 13-13.5 days of gestation.

Dose selection criteria:

Basis of dose selection: Decrease in plating efficiency.

Range finding studies: 13 concentrations ranging from 1 to 50,000 ng/ml. Each concentration used 10 dishes; the mean number of colonies developed in the control group: 39.3 with a mean plating efficiency ±S.D.: 21.8±3.8%.

$$\text{Plating Efficiency} = \frac{\text{No. of colonies/dish}}{\text{No. of target cells seeded/dish}} \times 100\%$$

Test Agent Stability: Not reported.

Metabolic activation system: NA.

Controls:

Negative control: 0.2% DMSO.
Positive control: benzo[a]pyrene, 5 µg/ml.

Exposure conditions:

Incubation and sampling times: 5-7 days; no sampling was conducted during the incubation period.
Doses used in the definitive study: 0.1, 1, 10, 50 and 100 ng/ml.
Study design: No. of replicates: 45 dishes/concentration with 25-45 colonies/dish.

Analysis:

Statistical analyses: Fisher's Exact test and Trend test if warranted.
Counting method: Steriomicroscope under blind conditions.

Criteria for positive results: A significant increase in the morphological transformation frequency for at least 2 dose levels compared to vehicle control or one dose showed a significant increase in the morphological transformation frequency.

Summary of individual study findings

Study validity: The study was valid to make an evaluation of [redacted] since the positive control was active.
Study outcome: In the dose range finding study, the highest concentration (100 ng/ml) produced a Relative Plating Efficiency of 46%, confirming that seen in the definitive study.
The results in the following table show that [redacted] was not genotoxic in the SHE Cell assay.

Treatment/ Concentration, ng\ml	Total No. of Colonies Scored	Total No. of Morphological Transformed Colonies	Morphological Transformation Frequency %	Relative Plating Efficiency %
Control	1799	4	0.22	100
[redacted]				
0.10	1806	4	0.22	100
1.0	2052	6	0.29	80
10.0	1810	0	0	55
50.0	1516	0	0	59
100.0	1465	1	0.068	46
[redacted]	1663	36	2.165[a]	104

[a] $P<0.05$

Genetic Toxicology Summary

At concentrations up to 100 ng/ml, [redacted], was inactive in the SHE Cell Assay.

Genetic Toxicology Conclusions

[redacted]; was not genotoxic in the SHE Cell Assay.

Recommendation

According to the ICH Guidelines (ICH Q3A and Q3B), the acceptance criterion for each impurity/degradant should be < 0.10% in the drug substance and < 1.00% in the drug product. In the Aerospan drug product, [redacted], a structure alert impurity/degradant, qualifies the proposed acceptance criterion up to 1.00% since it was not genotoxic in the SHE Cell Assay. In the drug substance, the acceptance criterion should be between 0.1% and 1% pending the chemist's review of the drug substance batch data relative to that of the drug product.

Reviewer's signature: _____
Lawrence F. Sancilio, Ph.D.

Supervisor's signature:

Concurrence - _____

cc: list: BRogers

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/s/

Lawrence Sancilio
5/28/03 01:25:48 PM
PHARMACOLOGIST

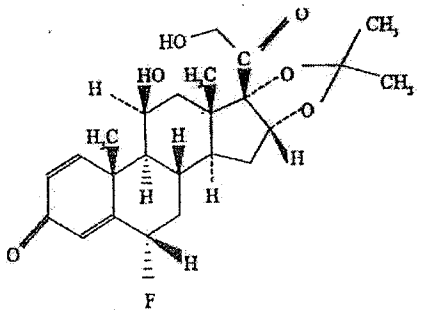
Joseph Sun
5/28/03 01:33:22 PM
PHARMACOLOGIST
I concur.

EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA

NDA No.: 21-247
Review No.: 4
Serial No./Type of Submission: N-000-BP; N-000-BZ
Dates of Submission: 10-11-01 and 12-7-01
Information to Sponsor: Yes (X), No ( )
Sponsor: Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311
Manufacturer for Drug Substance: ———————————

Reviewer: Lawrence F. Sancilio, Ph.D.
Division: PULMONARY AND ALLERGY DRUG PRODUCTS
HFD: 570
Reviewer Completion Date: 5/21/02
Drugs:

Trade Name: Aerobid.
Generic Name: Flunisolide Hemihydrate
Code Name: Unknown.
Chemical Name: Pregna-1, 4-diene-3, 20-dione, 6-fluoro-11, 21-dihydroxy-16, 17-[(1-methylethylidene) bis (oxyl)]-hemihydrate, (6α 11β, 16α)
CAS Registry No.: 77326-96-6
Mole File No.: Unknown
Molecular Formula/Molecular Weight: $C_{24}H_{31}O_6H$. ½ H_2O/443.51
Structure:



. 1/2 H_2O

Relevant, NDAs and DMFs: IND —— and 51,456, NDA 18-148 (flunisolide nasal solution) and 18-340 (flunisolide CFC MDI), and DMF ———————————

Drug Class: Glucocorticoid

Indication: Prophylactic and maintenance treatment of asthma in adult and children ≥ 4 years old.

Route of Administration; Daily Dose: Inhalation; Adults (≥ 12 years old) [redacted] mcg/day and children (4-11 years old), [redacted]

Proposed Use: Treatment of asthma.

Background

In the Dec. 7, 2001 submission, the sponsor proposed a [redacted] specification for the impurity, [redacted], in the flunisolide drug product. This report addresses the acceptability of this specification.

Evaluation

[redacted], an impurity/degradant, possesses a structural alert and requires a genotoxic evaluation. At the request of th e Agency, data for flunisolide in the mouse carcinogenicity assay was submitted (Aug. 28, 2001) to determine whether the results would qualify the specification of [redacted], for the impurity in the drug product. In the Oct. 11, 2001 submission, the sponsor at the request of the Agency indicated that the batch used throughout the mouse carcinogenicity assay contained [redacted]. In the Dec. 6, 2001 review of the August 28, 2001 amendment by L. Sancilio, the exposure of mice to the [redacted] in the flunisolide carcinogenicity assay was inadequate to support qualification of the proposed [redacted] specification in the drug substance. (Note: In the review, the [redacted] specification referred to the drug substance and not as stated in error to the drug product). Consequently, the proposed specification of [redacted] n the drug product is not acceptable and requires further study.

Recommendation

Since [redacted] possesses a structural alert, the compound alone should initially be evaluated for genotoxicity in the in vitro point mutation and chromosomal aberration assays. If active, the specification for the impurity in the drug product should be [redacted]%. If the [redacted] is not genotoxic, the [redacted] specification may be qualified following evaluation in a 3-month inhalation toxicity study in the most appropriate species.

Letter to the Sponsor

The proposed [redacted] specification for the impurity/degradant, [redacted] in the drug product is not acceptable and needs to be qualified. Since [redacted] possesses a structural alert, the compound alone should initially be evaluated for genotoxicity in the in vitro point mutation and chromosomal aberration assays. If active, the specification for the impurity in the drug product should be [redacted] %. If the [redacted] is not genotoxic, the [redacted] proposed specification may be qualified following evaluation in a 3-month inhalation toxicity study in the most appropriate species.

Reviewer's signature: _____
Lawrence F. Sancilio, Ph.D.
Supervisor's signature:

Concurrence - _____

cc: list: BRogers

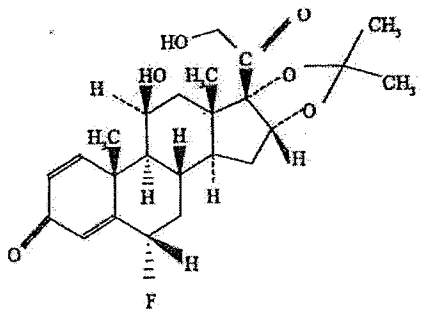
Attachment: 12/06/01 Review of 8/28/01 submission by L. Sancilio

EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA

NDA No.: 21-247
Review No.: 1
Serial No./Type of Submission: Amendment
Date of Submission: 8/28/01
Information to Sponsor: Yes (X), No ( )
Sponsor: Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311
Manufacturer for Drug Substance: ——————

Reviewer: Lawrence F. Sancilio, Ph.D.
Division: PULMONARY AND ALLERGY DRUG PRODUCTS
HFD: 570
Reviewer Completion Date: 12/06/01
Drugs:

Trade Name: Aerobid.
Generic Name: Flunisolide Hemihydrate
Code Name: Unknown.
Chemical Name: Pregna-1, 4-diene-3, 20-dione, 6-fluoro-11, 21-dihydroxy-16, 17-[(1-methylethylidene) bis (oxyl)]-hemihydrate, (6α 11β, 16α)
CAS Registry No.: 77326-96-6
Mole File No.: Unknown
Molecular Formula/Molecular Weight: $C_{24}H_{31}O_6H$. ½ H_2O/443.51
Structure:



. 1/2 H_2O

Relevant, NDAs and DMFs: IND —— and 51,456, NDA 18-148 (flunisolide nasal solution) and 18-340 (flunisolide CFC MDI), and DMF ——————

Drug Class: Glucocorticoid

Indication: Prophylactic and maintenance treatment of asthma in adult and children ≥ 4 years old.

Route of Administration; Daily Dose: Inhalation; Adults (≥ 12 years old) [redacted] mcg/day and children (4-11 years old), [redacted]

Proposed Use: Treatment of asthma.

Background

This amendment in a response to a request for data regarding the lots of flunisolide containing the impurity, [redacted], used in the mouse carcinogenicity assay. This interest was predominantly for the level of [redacted], which possesses a structural alert. Analysis of the results in the carcinogenicity assay was made to determine whether the proposed specification for this impurity would be qualified. The sponsor indicated that lot B3-1F-001 used in the mouse carcinogenicity assay contained [redacted]

Review and Evaluation

Lot B3-1F-001 analyzed by the sponsor for [redacted] by semiquantitative analysis indicated that it contained [redacted] of the impurity. The reviewing chemist after evaluating the data from this assay concluded that spiked samples containing [redacted] of the impurity actually contained less than [redacted] by an unknown amount. In evaluating the data for qualification, this reviewer analyzed the data assuming that the animals were exposed throughout the study to [redacted] present in the flunisolide lot.

In the carcinogenicity assay in mice, an increase in pulmonary adenomas occurred at 0.5 mg/kg; the NOEL for carcinogenicity was 0.05 mg/kg/day. The following calculations were made again assuming that the animals were exposed to the flunisolide containing [redacted] of the [redacted].

Daily exposure of animals to [redacted] at the oral NOEL of 0.05 mg/kg.

[redacted]

Determine the safe clinical inhalation dose from the oral NOEL by dividing the NOEL by the Safety Index [1000; 10 (for species difference) x 100 (for oral to inhalation route)] [redacted] (Safe Clinical Inhalation Dose Based on Preclinical data)

Determination of the clinical daily exposure to [redacted] from the daily dose of flunisolide

Adult dose of flunisolide: [redacted]
Exposure to [redacted] from the proposed specification of [redacted],

Children dose of flunisolide:
Exposure to from the proposed specification of

In analyzing the data in the rat carcinogenicity assay, an assumption was made that the animals were daily exposed to the impurity at % of the flunisolide dose. This was a conservative approach since the exposure was actually less than by an unknown amount. Based on the oral NOEL, the exposure of the impurity was 2-2.5 x the clinical exposure in adults and children to the clinical dose containing the proposed specification of ; this indicates no appreciable safety margin. Since pulmonary adenomas occurred following oral administration, it is conceivable that there may be greater sensitivity in the respiratory tract when the inhalation route is used to administer the compound. This is possible since in the carcinogenicity rat assay, N-nitrosodimethylamine by the oral route produced liver tumors, and by the inhaled route for 49-207 days produced nasal tumors and no liver neoplasms (Klein et al., Effects of long term inhalation of N- nitrosodimethylamine in rats, In: Relevance to human cancer of N-nitrosocompounds, tobacco smoke and mycotoxins, I.K. O'Neil, J. Chen and H. Bartsch (eds), Lyon, International Agency for Research on Cancer, pp 322-328, 1991). Further, taking into account factors relating the species (mouse vs human) and differences in route (oral vs inhalation), the safety margin falls well below one.

Recommendation

The proposed specification of % of in the flunisolide drug product was not acceptable based on the carcinogenicity data from the flunisolide batch containing of ; for qualification of this specification, should be inactive in the genotoxicity assays for point mutation and chromosomal aberration.

Letter to the Sponsor

We have reviewed your August 28, 2001 amendment to NDA 21-247. The oral mouse carcinogenicity study in which the flunisolide lot contained of showed pulmonary adenomas. Relating the oral NOEL and adjusting it for interspecies difference (rat vs human) and difference in route of administration (oral vs inhalation) to the clinical exposure of the proposed specification indicates no safety margin and consequently does not qualify. For qualification of this specification, the alone should be inactive in the genotoxicity assays for point mutation and chromosomal aberration.

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

cc: list: B. Rogers
L. Jafari

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/s/

Lawrence Sancilio
5/22/02 10:43:39 AM
PHARMACOLOGIST

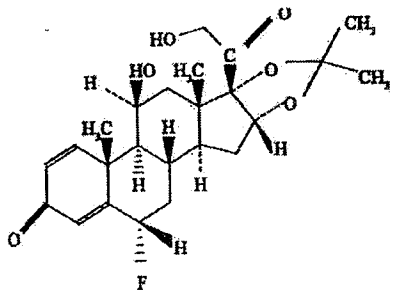
Joseph Sun
5/22/02 11:41:52 AM
PHARMACOLOGIST
I concur.

EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA

NDA No.: 21-247
Review No.: 1
Serial No./Type of Submission: Amendment
Date of Submission: 8/28/01
Information to Sponsor: Yes (X), No ( )
Sponsor: Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311
Manufacturer for Drug Substance: ———————————

Reviewer: Lawrence F. Sancilio, Ph.D.
Division: PULMONARY AND ALLERGY DRUG PRODUCTS
HFD: 570
Reviewer Completion Date: 12/06/01
Drugs:

Trade Name: Aerobid.
Generic Name: Flunisolide Hemihydrate
Code Name: Unknown.
Chemical Name: Pregna-1, 4-diene-3, 20-dione, 6-fluoro-11, 21-dihydroxy-16, 17-[(1-methylethylidene) bis (oxyl)]-hemihydrate, (6α 11β, 16α)
CAS Registry No.: 77326-96-6
Mole File No.: Unknown
Molecular Formula/Molecular Weight: $C_{24}H_{31}O_6H$. ½ H_2O/443.51
Structure:



. 1/2 H_2O

Relevant, NDAs and DMFs: IND —— and 51,456, NDA 18-148 (flunisolide nasal solution) and 18-340 (flunisolide CFC MDI), and DMF ————————————

Drug Class: Glucocorticoid

Indication: Prophylactic and maintenance treatment of asthma in adult and children ≥ 4 years old.

Route of Administration; Daily Dose: Inhalation; Adults (≥ 12 years old) [redacted] mcg/day and children ([redacted] years old), [redacted]

Proposed Use: Treatment of asthma.

Background

This amendment in a response to a request for data regarding the lots of flunisolide containing the impurity, [redacted] used in the mouse carcinogenicity assay. This interest was predominantly for the level of [redacted], which possesses a structural alert. Analysis of the results in the carcinogenicity assay was made to determine whether the proposed specification for this impurity would be qualified. The sponsor indicated that lot B3-1F-001 used in the mouse carcinogenicity assay contained [redacted]

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In the carcinogenicity assay in mice, an increase in pulmonary adenomas occurred at 0.5 mg/kg; the NOEL for carcinogenicity was 0.05 mg/kg/day. The following calculations were made again assuming that the animals were exposed to the flunisolide containing [redacted] of the [redacted]

Daily exposure of animals to [redacted] at the oral NOEL of 0.05 mg/kg.

0.05 mg/kg x [redacted]

Determine the safe clinical inhalation dose from the oral NOEL by dividing the NOEL by the Safety Index [1000; 10 (for species difference) x 100 (for oral to inhalation route)]
[redacted] (Safe Clinical Inhalation Dose Based on Preclinical data)

Determination of the clinical daily exposure to [redacted] from the daily dose of flunisolide

Adult dose of flunisolide: [redacted]
Exposure to [redacted] from the proposed specification of [redacted]

[redacted]

Children dose of flunisolide: [redacted]
Exposure to [redacted] from the proposed specification of [redacted]

[redacted]

In analyzing the data in the rat carcinogenicity assay, an assumption was made that the animals were daily exposed to the impurity at —% of the flunisolide dose. This was a conservative approach since the exposure was actually less than —% by an unknown amount. Based on the oral NOEL, the exposure of the impurity was 2-2.5 x the clinical exposure in adults and children to the clinical dose containing the proposed specification of [redacted]; this indicates no appreciable safety margin. Since pulmonary adenomas occurred following oral administration, it is conceivable that there may be greater sensitivity in the respiratory tract when the inhalation route is used to administer the compound. This is possible since in the carcinogenicity rat assay, N-nitrosodimethylamine by the oral route produced liver tumors, and by the inhaled route for 49-207 days produced nasal tumors and no liver neoplasms (Klein et al., Effects of long term inhalation of N- nitrosodimethylamine in rats, In: Relevance to human cancer of N-nitrosocompounds, tobacco smoke and mycotoxins, I.K. O'Neil, J. Chen and H. Bartsch (eds), Lyon, International Agency for Research on Cancer, pp 322-328, 1991). Further, taking into account factors relating the species (mouse vs human) and differences in route (oral vs inhalation), the safety margin falls well below one.

Recommendation

The proposed specification of [redacted] of [redacted] in the flunisolide drug product was not acceptable based on the carcinogenicity data from the flunisolide batch containing —% of [redacted] for qualification of this specification, [redacted] should be inactive in the genotoxicity assays for point mutation and chromosomal aberration.

Letter to the Sponsor

We have reviewed your August 28, 2001 amendment to NDA 21-247. The oral mouse carcinogenicity study in which the flunisolide lot contained —% of [redacted] showed pulmonary adenomas. Relating the oral NOEL and adjusting it for interspecies difference (rat vs human) and difference in route of administration (oral vs inhalation) to the clinical exposure of the proposed [redacted] specification indicates no safety margin and consequently does not qualify. For qualification of this specification, the [redacted] alone should be inactive in the genotoxicity assays for point mutation and chromosomal aberration.

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

cc: list: B. Rogers
L. Jafari

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/s/

Lawrence Sancilio
12/7/01 01:31:49 PM
PHARMACOLOGIST

Joseph Sun
12/7/01 04:08:29 PM
PHARMACOLOGIST
I concur.

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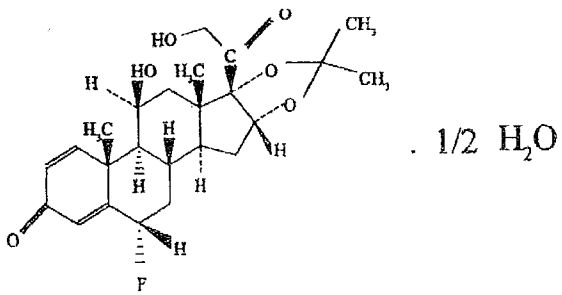
EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA

NDA No.: 21-247
Review No.: 0, **Original**
Serial No./Type of Submission: 0, Original
Date of Submission: 4/27/00
Information to Sponsor: Yes ( ), No (X)
Sponsor: Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311
Manufacturer for Drug Substance:

Reviewer: Lawrence F. Sancilio, Ph.D.
Division: PULMONARY AND ALLERGY DRUG PRODUCTS
HFD: 570
Reviewer Completion Date: 4/12/01

Drugs:

Trade Name: Unknown.
Generic Name: Flunisolide Hemihydrate
Code Name: Unknown.
Chemical Name: Pregna-1, 4-diene-3, 20-dione, 6-fluoro-11, 21-dihydroxy-16, 17-[(1-methylethylidene) bis (oxyl)]-hemihydrate, (6α 11β, 16α)
CAS Registry No.: 77326-96-6
Mole File No.: Unknown
Molecular Formula/Molecular Weight: $C_{24}H_{31}O_6H$. ½ H_2O/443.51
Structure:



. 1/2 H_2O

Relevant IND's, NDAs and DMFs: IND and 51,456, NDA 18-148 (flunisolide nasal solution) and 18-340 (flunisolide CFC MDI), and DMF

Drug Class: Glucocorticoid

Indication: Prophylactic and maintenance treatment of asthma in adult and children ≥ 4 years old.

Clinical Formulation

Composition:

Components	%w/w
Flunisolide Hemihydrate, USP	0.24
Absolute Ethanol USP	[redacted]
1,1,1,2-Tetrafluoroethane, Propellant HFA-134a	

The flunisolide HFA system is a cannister with a built in actuator/spacer. The spacer volume is approximately — ml, and the system delivers 120 doses. Each actuation delivers from the spacer 139 mcg/actuation of flunisolide hemihydrate; the dose delivered ex-spacer is — µg/actuation. The mass median aerodynamic diameter (MMAD) is about — µm, which is considerably larger than the flunisolide CFC product.

Route of Administration; Daily Dose: Inhalation; Adults (≥ 12 years old) [redacted] mcg/day and children (4-11 years old), 340 mcg/day.

Proposed Use: Treatment of asthma.

Disclaimer: Tabular and graphical information is from the sponsor's submission unless stated otherwise.

Studies Reviewed Within this Submission

None.

Studies Submitted that were Previously Reviewed in IND 51,456

Submission Date	Review Date	Reviewer
Aug. 29, 1996	Nov.18, 1996	S. Tripathi
Feb 25, and Mar. 24, 1998	Mar. 26, 1998	S. Tripathi
Oct. 4, 1999	Dec. 17, 1999	L. Sancilio

Single dose inhalation toxicity study in rats, T/5500/001, vol. 5.2, p 0-00052.

Single dose inhalation toxicity study in dogs, T/5500/002, vol. 5.3, p 0-00394.

Seven-day inhalation toxicity study in rats, T/5500/004, vol. 5.4, p 0-00667.

Seven-day inhalation toxicity study in dogs, T/5500/003, vol. 5.6, p 0-01410.

28-Day inhalation toxicity study in rats, T/5500/006, vol. 5.7, p 0-01837.

28-Day inhalation toxicity study in dogs, T/5500/007, vol. 5.9, p 0-02864.

13-Week inhalation toxicity study in rats, ANCTX08000, vol. 5.11, p 0-03243.

Response to FDA Inquiry, Ser. No. 80, submitted on 10/4/99 and reviewed by L. Sancilio on 4/6/00

OVERALL SUMMARY AND EVALUATION

Flunisolide is currently marketed as a metered dose inhaler (Aerobid) using three fluorinated hydrocarbons (trichloromonofluoromethane, dichlordifluoromethane and _____, CFC) as the propellant. The daily dosage is 1 mg for children 6-15 years old and 2 mg for adults. In this NDA, flunisolide is also administered by inhalation except that the propellant is HFA-134a instead of the CFC by the same sponsor. The advantage of the flunisolide HFA inhaler system was that the propellant does not deplete the ozone layer, and that the aerosol had a smaller particle size resulting in greater lung deposition and less oropharyngeal deposition. Consequently, the daily therapeutic dose of flunisolide HFA was lower than the flunisolide CAC. Since the two formulations differ in propellants, bridging studies were conducted to demonstrate comparable toxicity. The preclinical studies for flunisolide were summarized in NDA 18-148 and the final reports described in NDA 18-340. Bridging studies reviewed were acute, one- and four-week inhalation studies in rats and dogs (see 11/18/96 review of IND 51,456 by S. Tripathi) and a 13-week inhalation study in rats (see 3/26/98 review of IND 51,456 by S. Tripathi).

In the acute inhalation toxicity studies, the doses tested in rats were 2.4 mg/kg, 7.3 mg/kg and 8.5 mg/kg of the flunisolide- HFA formulation and 0.6 mg/kg, 3 mg/kg and 7.0 mg/kg of the flunisolide-CFC formulation and in dogs, 4.2 mg/kg of the flunisolide- HFA formulation and 4.6 mg/kg of the flunisolide-CFC formulation. In both studies decreased body weight gained were seen with both formulations.

In the 1-week inhalation toxicity studies, the doses tested in rats were 0.02 mg/kg, 0.1 mg/kg, 0.46 mg/kg, 1.79 mg/kg and 4.71 mg/kg of the flunisolide- HFA formulation and 0.72 and 4.08 mg/kg flunisolide-CFC formulation and in dogs, 0.3 mg/kg, 1.3 mg/kg and 4.0 mg/kg of the flunisolide- HFA formulation and 0.2 mg/kg and 3.5 mg of the flunisolide-CFC formulation. The toxicological profile characteristic of glucocorticoids in both formulations was similar in both species.

In the 4-week inhalation studies, the doses in rats were 0.0004 mg/kg, 0.01 mg/kg, and 0.069 mg/kg of the of the flunisolide- HFA formulation and 0.001 mg/kg and 0.087 mg/kg of the flunisolide-CFC formulation and in dogs, 0.03 mg/kg, 0.12 mg/kg and 0.44 mg/kg of the flunisolide- HFA formulation and 0.3 mg/kg and 0.36 mg/kg of the flunisolide-CFC formulation. In rats, there was no difference between the toxicity profile and the pharmacokinetics in the two formulations. In dogs, the toxiciological profile of both formulations was characteristic of glucocorticoids except that in the 0.069 mg/kg-

treated HFA M and F, alkaline phosphatase levels were increased approximately 2.8 X the controls. However, this was not accompanied by any histopathology. The flunisolide-HFA formulation was 26-40% less bioavailable than the flunisolide-CFC formulation.

In the 13-week inhalation bridging toxicity study, the doses in rats were: flunisolide-HFA, 0.001 mg/kg, 0.005 mg/kg and 0.02 mg/kg in the M and 0.0005 mg/kg, 0.001 mg/kg and 0.005 mg/kg and flunisolide-CFC, 0.001 mg/kg and 0.02 mg/kg in the M and 0.0005 mg/kg and 0.005 mg/kg in the F. The toxicity seen was characteristic of the glucocorticoids. However, it appeared that the corticosterone plasma levels were increased in the flunisolide hemihydrate HFA-treated M and F. This was attributed to high variability of the data. Further, the histological changes, characteristic of glucocorticoids, seen with both formulations were similar indicating that increased corticosterone plasma levels in the flunisolide hemihydrate HFA-treated animals were not formulation related (4/6/00 review by L. Sancilio). The HD of the flunisolide-CFC treated animals showed a greater effect on the hematology parameters than the HD flunisolide-HFA- treated animals with the exception of the eosinophil levels, which were decreased in the HD flunisolide-HFA- treated animals. In the review of 3/26/98 by S. Tripathi, the report was unaudited and no GLP statement was made. In the 12/17/99 review by L. Sancilio, the corrections and editorial changes made in the audited report did not change the conclusion that the two formulations were comparable. In the submitted report in the NDA, the GLP statement was included. Replacing the CFC formulation with HFA did not cause greater toxicity in rats over 13–week administration.

Safety Evaluation:

There were no safety concerns that were different from the marketed flunisolide CFC.

Safety issues relevant to clinical use:

The relevant safety issues are similar to the marketed flunisolide CFC.

Other clinically relevant issues:

None.

Conclusions:

Replacing the CFC propellant in the flunisolide aerosol formulation with HFA-134 poses no safety concern.

Communication review

Labeling review:

Additions are in **BOLD** and deletions are in ~~STRIKE OUT~~.

1 Page(s) Withheld

____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

____ Deliberative Process (b5)

OVERDOSAGE

Flunisolide hemihydrate infused intravenously at doses up to 4000 mcg/kg in mice, rats and dogs (approximately ——— **25, 50 and 170** times the maximum recommended daily inhalation dose ———————————) produced no mortality.

Recommendation

The NDA is approvable from a preclinical perspective with the above labeling revisions.

Lawrence F. Sancilio, Ph.D.

Attachments

Drug: **Flunisolide HFA**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric		0.085	4	0.34	18	0.0184	25	0.46
Adult	>12	0.085	8	0.68	50	0.0133	37	0.49

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	p.o.	0.5	3	1.5	3.05	3.26	3	3
rat	p.o.	0.0025	6	0.015	0.03	0.03	1/33	1/31
hamster			4	0	---	---	---	---
rat	p.o.	0.001	6	0.006	0.01	0.01	1/82	1/77
rat			6	0	---	---	---	---
Reproduction and Fertility:								
mouse			3	0	---	N/A	---	N/A
rat	p.o.	0.2	6	1.2	2.44	N/A	2	N/A
rat	p.o.	0.04	6	0.24	0.49	N/A	1/2	N/A
rat			6	0	---	N/A	---	N/A
Teratogenicity:								
mouse			3	0	---	N/A	---	N/A
rat	p.o.	0.2	6	1.2	2.44	N/A	2	N/A
rabbit	p.o.	0.04	12	0.48	0.98	N/A	1/1	N/A
rabbit			12	0	---	N/A	---	N/A
mouse			3	0	---	N/A	---	N/A
Overdosage:								
mouse	i.v.	4	3	12	24.39	26.09	25	25
mouse			3	0	---	---	---	---
rat	i.v.	4	6	24	48.77	52.17	50	50
rat			6	0	---	---	---	---
Other:	(Describe studies here)							
dog	i.v.	4	20	80	162.57	173.91	160	170
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

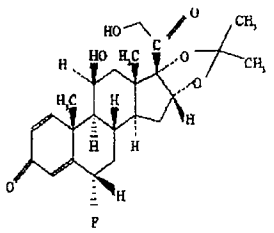
DIVISION OF PULMONARY DRUG PRODUCTS

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original, Review No. 1

IND Number:	51,456
Serial Number(s):	000
Date of Submission:	August 29, 1996
Date IND assigned to this Reviewer:	September 04, 1996
Information to the Sponsor:	Yes (X), No ( )
Reviewer:	Satish C. Tripathi, Ph.D.
Date of First Draft Review:	October 31, 1996
Date of Review Completed:	November 18, 1996
Sponsor:	Forest Laboratories, In., New York, NY (Dr. Michael Rosen: 212-421-7850)
Manufacturer (Drug Substance):	[redacted]
Drug Name: **Primary:**	Flunisolide (AEROBID) in HFA-134a
Other Names:	Aerobid HFA Flunisolide HFA Flunisolide HFA with AeroSpacer HFA-134a Flunisolide Hemihydrate MDI Aerobid (Flunisolide hemihydrate in HFA-134a) Inhaler System.
Secondary:	None.
Chemical Name:	6α-Fluoro-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with acetone, hemihydrate.
CAS Number:	77326-96-6

Structure:



. 1/2 H_2O

Molecular Weight and Formula: 443.51; $C_{24}H_{31}O_6F.1/2\ H_2O$

Related DMF: DMF for HFA-134a [redacted]

Pharmacological Class: Glucocorticoid

Indication: Asthma

Clinical Formulation: [redacted] 0.24% Solution (w/w) of Flunisolide hemihydrate, USP in [redacted] (w/w) 1,1,1,2-tetrafluoroethane (HFA-134a); [redacted] (w/w) dehydrated alcohol, and [redacted]

Route of Administration: Inhalation (oral) using metered-dose inhalation system

Previous Reviews:

Date of Submission	Reviewer	Review Date
08/29/96	Satish Tripathi	11/18/96
02/11/97	Satish Tripathi	02/24/97
08/26/97	Satish Tripathi	11/05/97

Studies Reviewed in this Submission:

TOXICOLOGY
Rat: 13-week Inhalation Toxicity Study with HFA Formulation

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

TOXICOLOGY

Rat: 13-week Inhalation Toxicity Study with HFA Formulation
[redacted] Unaudited Summary

Study Dates: October 29, 1997 to February 23, 1998
Testing Lab: [redacted]
Test Article: Flunisolide in CFC or HFA propellant supplied in aluminum MDIs.
GLP: GLP Statement not included.

METHODS

Species/Strain: Rats (strain not indicated).
Animals: 105/Sex (15/Sex/group) for main study and additional 18/Sex/group for determining plasma cortisone levels.
Route: Inhalation (Nose-only).
Dosage: HFA formulation: ♂: 0 (Vehicle Control); 1.0 µg/kg/day (LD); 5.0 µg/kg/day (MD); and 20 µg/kg/day (HD); ♀: 0, 0.5 µg/kg/day (LD); 1.0 µg/kg/day (MD), and 5.0 µg/kg/day (HD). CFC Formulation: ♂: 0 (Vehicle Control); 1.0 µg/kg/day (LD) and 20 µg/kg/day (HD); ♀: 0, 0.5 µg/kg/day (LD) and 5.0 µg/kg/day (HD).
Duration of Exposure: 30 minutes/day for 91 consecutive days.
Clinical Observations: Twice daily (once pre-exposure and once 1 to 2 hours post exposure).
Body Weights: Study Day 1 and weekly thereafter.
Food Consumption: Not determined.
Hematology: Blood samples collected on the day of necropsy.
Clinical Chemistry: Blood samples collected on the day of necropsy.
Urinalysis: Not done.
Plasma Corticosterone Levels: Satellite group animals: 30 minute post exposure on Day 1 or after 7 consecutive days of exposure at hourly intervals (3 rats/sex/dose group); Maximum blood sampling from each animal: 4-times. Main group animals: Week 4 and Week 12 at 2, 4, 6, 9, and 12 hours post exposure; One animal was bled only one time within each dose group.
Organ Weights, Gross- and Histopathology: All important organs were weighed; Histopathology was conducted on Control and HD groups only and was limited to adrenals, thymus, spleen, and respiratory tract.

RESULTS

Clinical Signs: No toxicologically significant treatment-related effects.

Mortality: There was one mortality which was attributed to accidental trauma; it was not indicated which group did this animal belong to. This could be considered as not drug related.

Body Weights: Treatment resulted in decreased bodyweight gains in males (HFA: LD 9%, MD 13%, HD 59%; CFC: LD 28%, HD 81%) and decreased bodyweight gains (HFA: LD 42%, MD 54%; CFC: LD 40%) and body weight loss (HFA: HD 3%; CFC: HD 9%) in females.

Hematology: As shown in Table 1, treatment resulted in increased values of total leukocyte counts in both the HFA and the CFC groups; however, extent of increase was slightly more in CFC groups than in HFA groups. Platelet counts decreased in the CFC group but not in the HFA group. Changes in WBC differential counts (increased segmented neutrophils and monocytes and decreased lymphocytes) were more severe in CFC groups than in HFA groups. Decreased Eosinophils were seen in all the groups with females treated with HFA and HD group males treated with CFC formulation.

Table 1. Hematology Findings in a 13-wk Rat Inhalation Toxicity Study

Hematology		**% Change over Vehicle Control values**				
Parameters		**HFA Groups**			**CFC Groups**	
		LD	**MD**	**HD**	**LD**	**HD**
Total Lukocytes ↑	♂	17%		23%	19%	36%
	♀	21%	16%	33%	24%	46%
Platelet Counts ↓	♂					10%
	♀					20%
Segmented Neutrophils ↑	♂			31%		36%
	♀					77%
Monocytes ↑	♂			3.6-fold		3.5-fold
	♀			44%		4-fold
Lymphocytes ↓	♂	18%		36%	12%	56%
	♀	21%	14%	37%	28%	67%
Eosinophils ↓	♂					12%
	♀	12%	12%	50%		

Clinical Chemistry: Increase in the levels of ALT, AST, lactate dehydrogenase, and tryglycerides were comparable in HFA and CFC groups.

Plasma Corticosterone Levels: No toxicologically significant treatment-related effects.

Organ Weights: No toxicologically significant treatment-related effects.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Typical steroid effects on lymph nodes, thymus, spleen, and adrenal glands were present in both HFA as well as CFC groups and were comparable (See Table 2). Incidence of alveolar histiocytosis was slightly more in the groups exposed to CFC formulation than those exposed to HFA formulation. Degree of severity of histopathologic changes was comparable in the groups exposed to HFA and CFC formulations.

Table 2. Histopathologic Findings in a 13-wk Rat Inhalation Toxicity Study

Organ	HFA: Veh. Control	HFA: HD	CFC: Veh. Control	CFC: HD
Lung: Alveolar histiocytosis:				
Males	5	2	2	8
Females	0	3	2	4
Lymph Node: Lymphoid depletion:				
Males	3	10	11	10
Females	3	10	7	8
Thymus: Lymphoid depletion:				
Males	2	15	5	14
Females	4	14	1	15
Spleen: Lymphoid depletion:				
Males	2	9	3	13
Females	0	6	3	15
Adrenal Gland: Cortical atrophy:				
Males	0	11	1	9
Females	0	5	1	7

SUMMARY AND EVALUATION

The objective of this 13-wk rat inhalation toxicity (bridging) study was to compare toxicity profile of the HFA and the CFC formulations of the drug and establish that replacement of CFC formulation by HFA formulation does not impose any additional safety concerns. Data from this study have shown that administration of top doses of both formulations of the drug resulted in sufficient toxicity as shown by decrease in bodyweight gains (all dose groups except HD females) or body weight loss (HD female groups only). Changes in hematology, clinical chemistry, and histopathology were either more severe in CFC groups than those in HFA groups or were comparable between the two groups. Therefore, this study has shown that the replacement of CFC formulation by HFA formulation does not impose additional safety concerns when given for 13 weeks in rats. The sponsor should provide complete report of the study together with a statement of compliance with GLP.

RECOMMENDATION

The 13-week inhalation toxicity study in rats has shown that replacement of CFC formulation by HFA formulation does not impose additional safety concerns. The sponsor should provide complete report of the study together with a GLP Statement.

Comments to the Medical Reviewer: The 13-wk inhalation toxicity (bridging) study in rats has shown that replacement of CFC formulation by HFA formulation does not impose additional safety concerns.

Comments to the Sponsor: Your submissions of February 25, 1998 and March 24, 1998 regarding 13-week inhalation toxicity bridging study in rats are acceptable. Please provide complete report of the study together with a statement of compliance with good laboratory practice.

3/26/98

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

Concur March 26, 1998

Original IND
C.C. HFD-570/Division File
HFD-570/Joseph Sun, Team Leader (Pharmacology-Toxicology)
HFD-570/Peter Honig, Medical Reviewer and Team Leader
HFD-570/Sandra Barnes, Project Manager
HFD-570/Satish Tripathi, Pharmacology-Toxicology Reviewer

SUMMARY AND EVALUATION

The objective of this 13-wk rat inhalation toxicity (bridging) study was to compare toxicity profile of the HFA and the CFC formulations of the drug and establish that replacement of CFC formulation by HFA formulation does not impose any additional safety concerns. Data from this study have shown that administration of top doses of both formulations of the drug resulted in sufficient toxicity as shown by decrease in bodyweight gains (all dose groups except HD females) or body weight loss (HD female groups only). Changes in hematology, clinical chemistry, and histopathology were either more severe in CFC groups than those in HFA groups or were comparable between the two groups. Therefore, this study has shown that the replacement of CFC formulation by HFA formulation does not impose additional safety concerns when given for 13 weeks in rats. The sponsor should provide complete report of the study together with a statement of compliance with GLP.

RECOMMENDATION

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Comments to the Medical Reviewer: The 13-wk inhalation toxicity (bridging) study in rats has shown that replacement of CFC formulation by HFA formulation does not impose additional safety concerns.

Comments to the Sponsor: Your submissions of February 25, 1998 and March 24, 1998 regarding 13-week inhalation toxicity bridging study in rats are acceptable. Please provide complete report of the study together with a statement of compliance with good laboratory practice.

3/26/98

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

Original IND
C.C. HFD-570/Division File
HFD-570/Joseph Sun, Team Leader (Pharmacology-Toxicology)
HFD-570/Peter Honig, Medical Reviewer and Team Leader
HFD-570/Sandra Barnes, Project Manager
HFD-570/Satish Tripathi, Pharmacology-Toxicology Reviewer

DIV FILE
MAR 26 1998

DIVISION OF PULMONARY DRUG PRODUCTS

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Review No. 4

IND Number:	51,456
Serial Numbers:	
Dates of Submission:	February 25, 1998 and March 24, 1998
Dates of Assignment:	March 13, 1998 and March 25, 1998
Information to the Sponsor:	Yes (X), No ( )
Reviewer:	Satish C. Tripathi, Ph.D.
Date of Review Completed:	March 26, 1998
Sponsor:	Forest Laboratories, Inc., New York, NY (Dr. Michael Rosen: 212-421-7850)
Manufacturer (Drug Substance):	[ ]
Drug Name: Primary:	Flunisolide (AEROBID) in HFA-134a
Other Names:	Aerobid HFA Flunisolide HFA Flunisolide HFA with AeroSpacer HFA-134a Flunisolide Hemihydrate MDI Aerobid (Flunisolide hemihydrate in HFA-134a) Inhaler System.
Secondary:	None.
Chemical Name:	6 -Fluoro-11 , 16 , 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with acetone, hemihydrate.
CAS Number:	77326-96-6

21 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

REVIEW AND EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA

Key Words: Final Report

Reviewer: Lawrence F. Sancilio, Ph.D.

Division: PULMONARY DRUG PRODUCTS, HFD-570

Reviewer Completion Date: 12/17/99

IND No. 51456

Serial No. /Date/ 80, 10/4/99

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

Sponsor: Forest Laboratories, Incorporated
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Drug: flunisolide hemihydrate

Drug Class: Glucocorticoid

In this submission, the sponsor listed the differences between the audited (9/11/98, vol. 10.1 and 10.2) and unaudited (2/25/98, vol. 5.1) reports (N002318B) on the 13-week inhalation toxicity study in rats comparing Aerobid HFC with Aerobid CFC. The unaudited report was a summary of the data; line listings were only provided with the microscopic findings.

The corrections and editorial changes made in the audited report do not change the conclusion that the two formulations were comparable.

Recommendation

The conclusion from the unaudited report was acceptable upon evaluating the changes made in the audited report.

Lawrence F. Sancilio 12/17/99
Lawrence F. Sancilio, Ph.D.
Dec. 17, 1999

IND 51,456
cc. /HFD-570 Division File
/HFD-570 DOHearn
/HFD-570 LSancilio
/HFD-570 CSO

SANCILIO

6 2000

REVIEW AND EVALUATION OF PHARMACOLOGY/ TOXICOLOGY DATA

Key Words: Final Report

Reviewer: Lawrence F. Sancilio, Ph.D.

Division: PULMONARY DRUG PRODUCTS, HFD-570

Reviewer Completion Date: 4/6/00

IND No. 51,456

Serial No. /Date/ 80, 10/4/99

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

Sponsor: Forest Laboratories, Incorporated
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Drug: flunisolide hemihydrate

Drug Class: Glucocorticoid

In this submission, the sponsor responded to our inquiry at the PRE-NDA teleconference for flunisolide hemihydrate HFA, whererby the corticosterone levels in the flunisolide hemihydrate-HFA-treated animals showed an increase while those in the flunisolide hemihydrate-CFA-treated animals manifested the expected decrease in the corticosterone plasma levels. However, both preparations, histologically, produced the following effects characteristic of hyperglucocorticoidism: increased incidence of thymus lymph depletion, lymphoid depletion in spleen, and cortical atrophy of the adrenal glands.

The sponsor attributed the apparent increase in the corticocosterone levels due to the high variability. To show this, the corticosterone levels were submitted in figures and as a bar graph. The corticosterone levels in the control and treated animals were presented on days 1, 7, 14, 28 and 90. The levels on day 1 were markedly variable. In all the HFA studies, the levels decreased with time, with the decrease being greater in the treated animals. Thus, the apparent increase in corticosterone levels was attributed to the high variability. Further, in both formulations, the histopathology with respect to glucocorticoid effects was similar.

Recommendation

There is no concern for the apparent increase in the corticosterone levels in the flunisolide hemihydrate-HFA-treated animals. This was due to high variability. The flunisolide hemihydrate-HFA and-CFA formulations were not different.

Lawrence F. Sancilio 4/6/02
Lawrence F. Sancilio, Ph.D.

Clyde Jopkston April 6, 2002

IND 51,456
cc. /HFD-570 Division File
/HFD-570 MPurucker
/HFD-570 LSancilio
/HFD-570 CSO

Approved by Dr. J. Sun

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Sancilio
4/16/01 02:53:47 PM
PHARMACOLOGIST

Joseph Sun
4/19/01 12:34:05 PM
PHARMACOLOGIST
I concur.