

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-784

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 20-784

Drug name: Nasacort HFA (triamcinolone acetonide) Nasal

Sponsor (or agent): Aventis Pharmaceuticals, Inc.

Indication: Treatment of nasal symptoms of seasonal and perennial rhinitis in adults and children 6 years of age and older.

Division name: Division of Pulmonary and Allergy Drug Products

Reviewer name: Timothy J. McGovern, Ph.D.

Regulatory recommendation: AP

Date: March 4, 2004

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EXECUTIVE SUMMARY

1. Recommendations

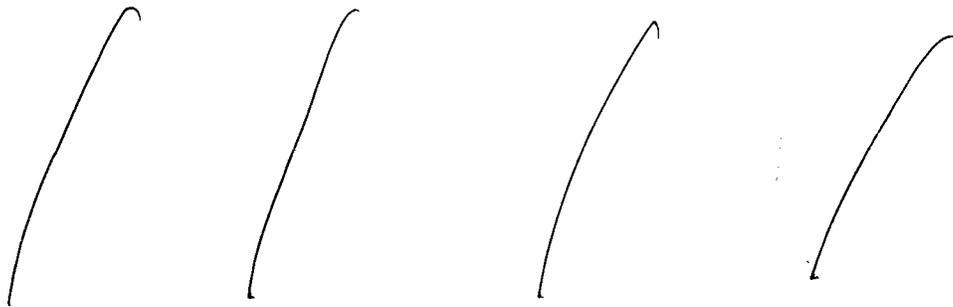
1.1 Recommendation on approvability

This application is recommended for approval from a nonclinical perspective.

1.2 Recommendation for nonclinical studies

None at this time.

1.3 Recommendations on labeling



2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

See original NDA review by Dr. Luqi Pei, dated October 4, 1997.

2.2 Pharmacologic activity

See original NDA review by Dr. Luqi Pei, dated October 4, 1997.

2.3 Nonclinical safety issues relevant to clinical use

None at this time.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 20-784

Review number: 2

Sequence number/date/type of submission: 000/January 9, 2004/BL
000/February 23, 2004/BP

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Aventis Pharmaceuticals, Inc., Bridgewater, NJ

Manufacturer for drug substance: same

Reviewer name: Timothy J. McGovern, Ph.D.

Division name: Pulmonary and Allergy Drug Products

HFD #: 570

Review completion date: February 5, 2004

Drug:

Trade name: NASACORT[®] HFA Nasal Aerosol

Generic name: triamcinolone acetonide

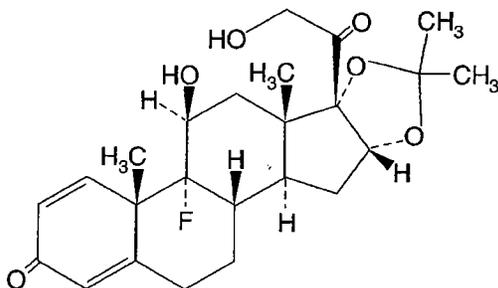
Code name: NA

Chemical name: 9-Fluoro-11 β ,16 α ,17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16,17-acetal with acetone

CAS registry number: NA

Molecular formula/molecular weight: C₂₄H₃₁FO₆/434.5

Structure:



Relevant INDs/NDAs/DMFs: NDAs 19-798 (Nasacort Nasal Inhaler); 20-468 (Nasacort AQ); 18-117 (Azmacort Oral Inhaler);
43,841:

Drug class: Glucocorticosteroid

Indication: Treatment of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 6 years of age and older

Clinical formulation: Microcrystalline suspension of triamcinolone acetonide in tetrafluoroethane (HFA-134a) and dehydrated alcohol USP 0.7% w/w. Each canister contains 15 mg of triamcinolone acetonide, — ng dehydrated alcohol, and — , HFA-134a. Each actuation meters 100 mcg of triamcinolone acetonide in 65 mg of suspension from the valve and delivers 55 mcg of triamcinolone acetonide from the nasal actuator to the patient after an initial priming of 3 actuations. There are 100 label claim actuations in one Nasacort HFA canister.

Route of administration: Intranasal

Proposed use:

The recommended starting dose of Nasacort HFA is 220 mcg per day given as two sprays (55 mcg/spray) in each nostril once daily. Once the maximal effect has been achieved, it is always desirable to titrate the patient to the minimum effective dose.

Nasacort HFA is not recommended for children below 6 years of age since adequate numbers of patients have not been studied in this age group.

Individualization Of Dosage: Individual patients will experience a variable time to onset and degree of symptom relief when using intranasal triamcinolone acetonide. It is recommended that dosing be started at 220 mcg (2 sprays in each nostril) once a day in patients age 6 years of age and older and the effect be assessed in four to seven days.

Statistically significant relief of some patient symptoms may be seen within the first day of treatment. If greater effect is desired, an increase of dose to 440 mcg once a day can be tried in adults and adolescents age 12 and older. If adequate relief has not been obtained by the third week of treatment, alternate forms of treatment should be considered.

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

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

This review is focused on the adequacy of the proposed product label. Nasacort has previously been approved in an aqueous formulation and a nonclinical review of NDA 20-784 was finalized on October 4, 1997 by Dr. Luqi Pei; the application was concluded to be approvable pending resolution of issues related to impurities and extractables. These issues have been resolved (see various CMC consults).

3.2 PHARMACOLOGY

Not applicable.

3.3 PHARMACOKINETICS/TOXICOKINETICS

Not applicable.

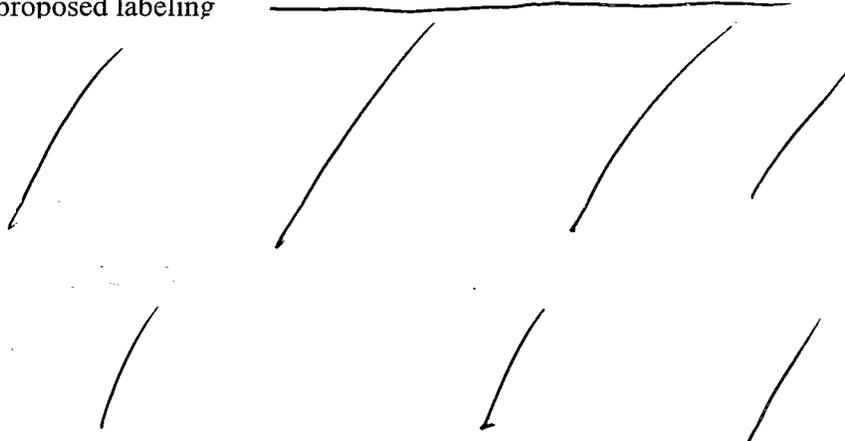
3.4 TOXICOLOGY

Not applicable.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Nasacort has previously been approved in an aqueous formulation and a nonclinical review of NDA 20-784 was finalized on October 4, 1997 by Dr. Luqi Pei; it was concluded that the application was approvable pending resolution of issues related to impurities and extractables. These issues have been resolved (see various CMC consults).

This review is focused on the proposed nonclinical sections of the product label. The sponsor's proposed labeling



Unresolved toxicology issues (if any): None at this time.

Recommendations:

This application is recommended for approval from a nonclinical perspective pending incorporation of recommended edits to the product label.

3 Page(s) Withheld

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 Draft Labeling

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/s/

Timothy McGovern
3/4/04 02:48:12 PM
PHARMACOLOGIST

**PHARMACOLOGY/TOXICOLOGY REVIEW FOR
CHEMISTRY CONSULT REQUEST**

Application Information

NDA number: 20-784
Drug Name: Nasacort® HFA (Triamcinolone acetonide)
Sponsor and/or agent: Aventis
Date of submission: 06-OCT-03, 05-AUG-03, and 02-SEP-03

Request Information

Request Subject Safety evaluation of leachables, extractables & particulates
Request Initiator Dr. Craig Bertha
Request Date September 24, 2003

Reviewer Information

Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Drug Products
Division Code: HFD-570
Review Completion Date: October 22, 2003

Summary: This review evaluates the safety of foreign particulates and three leachables/extractables present in Nasacort HFA. The leachables and extractables are _____
_____ The proposed specification for the particulate is _____. The proposed leachable specifications are _____ canister (detection limits) for _____ respectively. The proposed extractable specifications are _____ respectively. The review finds that the proposed specifications for the particulates and leachables are acceptable.

REVIEW

Dr. Craig Bertha requested the safety evaluation of foreign particulates in a consult request dated September 24, 2003. This request addresses the submission of August 5, 2003.

The review of leachables and extractable evaluates the adequacy of the sponsor's responses to the nonclinical comments (Item 3) in 24-SEP-2003 approvable letter (DFS file name description: 20784 September 2003 AE letter). These comments were originated in Dr. L. Pei's review dated July 17, 2003. They were also conveyed to the Sponsor on August 13, 2003 via a facsimile. Both 02-SEP-03 and 06-OTC-03 submissions respond to the comments. _____

“Provide data demonstrating that the following three potential _____ leachables are not present in the formulation of the drug product during shelf life: _____ Alternatively, you may tighten your criteria for these _____ extractables and provide qualification data supporting the lower limits. For _____ additional qualification data are not needed if it is shown that the concentration of this potential leachable would not exceed _____/canister during the product shelf life.”

Sponsor’s response to the Division’s comment on the specification for _____ is satisfactory. The Division asked the sponsor to demonstrate that this chemical is not present during the product shelf life. Data in 02-SEP-03 submission shows that no _____ is detected at _____ of storage at room temperature (limit of detection = _____/canister).¹ The sponsor also tightens the specification for _____ in the _____ from _____ to _____. Also, Dr. Craig Bertha indicates that the Division is considering granting a shelf life of 15 months for the product. The specification for _____ is no longer an outstanding issue.

Sponsor’s response to the Division’s comment on the specification for _____ is satisfactory. The Division asked the sponsor to demonstrate that this chemical is not present during the product shelf life. Data in 02-SEP-03 submission shows that no _____ is detected at _____ of storage at room temperature (limit of detection = _____/canister). The sponsor also tightens the specification for _____ from _____ mg/g to _____ mg/g. The specification for _____ is no longer an outstanding issue.

Sponsor’s response to the Division’s comment on _____ is satisfactory. The sponsor states that the level of _____ after _____ of storage in room temperature is below the detection limit of _____ canister. Such a level of the compounds is in compliance with the Division’s recommendation of less than _____/canister. The specification issue of _____ has been resolved.

Particulates

Dr. Craig Bertha requested non-clinically the safety evaluation of foreign particulates present in Nasacort® HFA (consult request dated 24-SEP-03). The estimated maximum daily exposure of the particulates is _____ patient (from _____). This corresponds to a dose of _____ µg/kg/day on a body weight basis. This dose is smaller than the qualification threshold of _____

¹ A specification of 100 µg/canister corresponds to a daily exposure of 114 ng/kg for a 50-kg patient receiving 8 actuations of the drug. Each canister contains 140 actuations of the drug.

µg/kg/day currently used by the Division. It is also much smaller than the EPA standard for unknown particulate matters (PM_{2.5}) of 6 µg/kg/day (based on the annual average PM_{2.5} of 15 µg/m³ and a daily breathing air volume of 20 m³ for a 50-kg individual. The specification of _____ (corresponding to a daily dose of _____) is considered qualified.

Conclusion:

The newly proposed specifications for _____ and particulates are acceptable. Table 1 lists these specifications:

Table 1. Permissible Specifications for several Extractable/Leachables in Nasacort HFA

Compound	Permissible Specifications		
	Extractable	Leachable ^a	Other
/ /	/ /	/	-
Particulates	-		/ /

a. Detection limit.

Luqi Pei, Ph.D.
Pharmacologist

Timothy McGovern, Ph.D.
Supervisory Pharmacologist

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/s/

Luqi Pei
10/24/03 08:08:50 AM
PHARMACOLOGIST

Timothy McGovern
10/27/03 04:23:32 PM
PHARMACOLOGIST
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: (Division/Office) T. McGovern, HFD-570			FROM: Craig M. Bertha/HFD-820	
DATE 9/24/03	IND NO.	NDA NO. 20-784	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 8/7/03 (assigned 8/8/03)
NAME OF DRUG Nasacort HFA (triamcinolone acetonide) Nasal Aerosol		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE PDUFA date of 9/7/03
NAME OF FIRM: Aventis Pharmaceuticals, Inc. (US Agent is Quintiles)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (Specify below)				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary): See attached sheet. cc: Orig. NDA # 20-784 HFD-570/CBertha HFD-570/Div. File HFD-570/GPoochikian HFD-570/LPei/VWhitehurst HFD-570/CJackson/SBarnes				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

Consult Request

Please evaluate the toxicological adequacy of the response to comment 2.d. In summary the applicant has a limit of not more than — foreign particles. This is equated to be equivalent to — of potential maximum daily intake (see assumptions and calculations on p. 040).

The applicant is referring to literature data to conclude that the ' — , exposure is “significantly below the levels of particulates considered safe” and that this justifies their “removal of the requirement for toxicological assessment of the foreign particulates in the” drug product.

See attached full response to our original query.

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Guiragos Poochikian
9/24/03 10:27:41 AM

PHARMACOLOGY/TOXICOLOGY REVIEW
FOR
CHEMISTRY CONSULT REQUEST

Application Information

NDA number: 20-784
Drug Name: Nasacort[®] HFA (Triamcinolone acetonide)
Sponsor and/or agent: Aventis
Date of submission: March 21, 2003

Request Information

Request Subject Safety evaluation of leachables and extractables
Request Initiator Dr. Craig Bertha
Request Date April 21, 2003

Reviewer Information

Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Drug Products
Division Code: HFD-570
Review Completion Date: July 17, 2003

This review evaluates the safety of leachables and extractable in Nasacort[®] HFA.¹ Nasacort[®] HFA contains 12 extractables and 3 leachables. The leachables were also identified as extractables. The review considers all extractables as potential leachables.² The review finds that there is sufficient information to support the safety of the proposed specifications for nine compounds, but insufficient information for the remaining three compounds. These three compounds are _____ (particularly _____). The review recommends the following two options: 1) providing evidence indicating that these compounds are not present as leachables at the shelf life of the product, 2) lowering their specifications and providing evidence to support the safety of the new specifications.

The review conducts the safety evaluation of the leachables by comparing their acceptable daily intake values (ADIs) with the expected corresponding daily exposure from the current application. The review considers the leachable qualified if its expected level of daily exposure is below the ADI. The review uses the ADIs previously set by the Division whenever possible.

¹ The leachables are defined as the compounds actually found in the drug product formulation during shelf life. The extractables are compounds extracted by special methodology from the incoming product container closure components. Components of interest in this product are the _____

² The sponsor has not determined whether the remaining extractables are present as leachables in the final drug product. It is conceivable that the extractables might be present as leachables because HFA is a lipophilic solvent and it may extract certain compounds from the device. The review, therefore, considers all extractables as potential leachables.

For compounds that the ADIs have not been set and have no signals for concerns about their mutagenicity, carcinogenicity and irritation, the review uses the current divisional practice of the qualification threshold of a total daily exposure

The safety evaluation in this review is based on a worse case scenario of the daily exposures. When a compound is reported as both leachable and extractable, its daily exposure is based on the leachable concentrations. The review uses the following parameters to derive the expected daily exposure of leachables in humans: the maximum recommended dose of 8 actuations for a 50-kg patient and 140 actuations/canister.^{3,4}

The review uses non-proprietary information to set ADIs for the leachables. Information sources are given in reference citations.

Leachables:

Levels of leachables in Nasacort[®] HFA are acceptable. Three leachables were identified in the product. They are [redacted]. The expected daily exposure level was [redacted] μg/kg/day for [redacted] respectively⁵. These expected exposure levels are smaller than their respective ADIs of [redacted] μg/kg/day. (See Dr. L. Pei review [redacted] and the current review for [redacted] (later). The specification for the leachables, therefore, is allowable.

Extractables:

Nasacort[®] HFA contained a number of extractables. They are [redacted]. Sources of the extractables are the [redacted]. Table 1 (next page) presents the estimated daily exposure, the ADIs, and safety margins for these compounds.

1. [redacted] No animal toxicity data was found for [redacted]. A database named the Chemical Carcinogenesis Research Information System (CCRIS) shows that [redacted] tests positive in the mouse lymphoma L5178Y cell in the absence of the S9 fraction at concentrations of [redacted], and negative in the presence of the S9 fraction. The compound was also negative [redacted].

³ The proposed labeling states: "The recommended starting dose of Nasacort HFA is 220 μg per day as two actuations (55 μg/spray) in each nostril. If needed, the dose may be increased to 440 μg once a day (55 μg/spray)..."

⁴ Each canister is designed to deliver 100 actuations but is filled with a total of [redacted] actuations.

⁵ Each canister contains [redacted] for [redacted] respectively.

in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538.

The relevance of these data in the safety evaluation of the compound in the Nasacort[®] HFA is unknown. Overall, available data is insufficient for a sound safety evaluation of _____ in the drug product.

Table 1. Extractables and Their ADIs in Nasacort[®] HFA

Compound	Concentration (µg/canister)	Exposure (µg/kg/day)	ADI (µg/kg/day)	Safety Margin

1, The review of L. Pei dated January 27, 2000 in NDA 20-784.

2. Review of L. Pei²

3. The current review

4. Dr. L. Sancilio's review dated 16-MAR-1995 in NDA 20-236

2.

The level of this extractable is acceptable. The expected daily exposure of _____ is _____. The ADI for this compound is _____ (see Dr. L. Pei's review _____).⁶ This ADI was derived from the NOAEL of _____ in the _____ study in the older version. The additional data in the most recent version (updated on 14-FEB-2003) shows that _____. A dermal sensitization and irritation test shows that the compound is not irritating or allergic. Available data suggest that the compound may be non-carcinogenic and non-mutagenic. It is reasonable to set the ADI at _____ by applying an uncertainty factor of 1,000 for extrapolating from rat oral exposure to human inhalation.

⁶ Table 1 of Dr. L. Pei's review _____ incorrectly listed the ADI value as _____ although the text identified it as _____

and the Material Safety Data Sheet (MSDS) provided by the sponsor. The MSDS indicates that the manufacturer's ADI is /day. A literature search indicates that the toxicity profile of has been well characterized. Its carcinogenicity (oral) and reproductive toxicity, including teratogenicity of the compound has been tested for the carcinogenicity studies). The ADI of /day was more conservative from the safety point of view.

8. The level of this extractable is acceptable. The expected maximum exposure to is /kg/day. This level is lower than the qualification threshold of /day. Note that the Division previously set the ADI at based on EPA's standard for. See Dr. L. Pei review dated. The current review revises the ADI down to /day.

9. The proposed specification for is acceptable. The expected maximum exposure of patients to is lower than kg/day. The level is lower than the ADI of /day (Dr. L. Sancilio's review dated 05-MAR-1995 in NDA 20236 and based on publically available data). The current review, thus, omits the safety evaluation of the individual compound, but provides specifications for for future reference (Table 2, below).

Table 2 Nasocort® HFA

Compound	Concentration (ng/canister)	Exposure (ng/kg/day)
/	/	/

10. The level of this extractable is acceptable. is detected both as a leachable and an extractable. The expected exposure to the compound is μg/kg/day as extractable and leachable, respectively. The current review sets an ADI at ag/kg/day. This value is derived from the OSHA's of. That corresponds to a daily exposure of mg/kg/day based on a breathing volume of 10 cm³ for a 60-kg person in 8 hours. An ADI for this compound can be set at mg/kg/day by application an uncertainty factor of 10 that covers healthy to general

⁷ Hazardous Material data bank, updated 08-NOV-2002.

population. Note that Dr. L. Pei review _____ set an ADI of _____ $\mu\text{g}/\text{kg}/\text{day}$.

11 _____
The specification for the _____ is not acceptable. The application did not contain adequate information to support the safety of expected exposure of patients to _____. The application has identified _____ as the extractables. (_____ the source of the extractables.) Table 3 (below) provides a list of the extractables. The application has proposed specifications for _____ ($\mu\text{g}/\text{canister}$). _____ The review considers the worst case scenario that _____ Thus, the review uses _____ $\text{ng}/\text{kg}/\text{day}$ as the expected the maximum exposure level _____

Table 3

a

Based on publically available data, Dr. Sancilio determined ADI's for these _____ (see his review dated 20-NOV-1996 in NDA 20-486). The ADI vary significantly, almost by 260 folds. For example, the ADI for _____ is _____ $\text{ng}/\text{kg}/\text{day}$ while for _____ With the exception of _____ the ADI for the _____, in the application, was _____ kg/day or greater. The expected daily exposure of _____ in the current application is up to _____, a value smaller than their ADIs, and is acceptable. _____ however, is an exception. Patient's exposure to this compound is greater than its ADI. It may be possible that the expected exposure for _____ is below its ADI, _____ At present, the available data does not support the expected level of _____

12.

The level of this extractable is acceptable. The expected exposure to _____ in the application is _____/day, a value lower than the ADI of _____/day (See Dr. L. Pei review _____). Dr. Pei's review was based on nuisance particulate limit. This limit is reasonable as the compound is non-carcinogenic. The _____ (updated on 14-JAN-2002) states: "Chronic feeding studies of rats at dietary levels up to _____) for 2 years did not show any evidence of adverse effects. In another study, mice were fed _____ of the diet for 80 weeks. Macro and microscopic exam of these animals found no significant increase in malignant or benign tumors, nor was there any significant increase in mortality."

Conclusion:

The sponsor has not provided sufficient data to qualify the proposed level of these three extractables in Nasacort® HFA: _____

_____ The sponsor should be informed to either provide data to support the qualification of these extractables, or lower their levels in the drug product.

Recommendation:

The sponsor needs to provide data showing the following three compounds are not present at the shelf-life of the drug product: _____

_____ Alternatively, the sponsor may lower their specifications and provide data to support the new specifications. For _____, additional data is not needed if the sponsor shows that its concentration as extractable at the end of shelf life is below _____ µg/canister.

Luqi Pei, Ph.D. 7/17/03
Pharmacologist

Joseph Sun, Ph.D. 7/17/03
Supervisory Pharmacologist

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/s/

Luqi Pei
7/17/03 01:39:52 PM
PHARMACOLOGIST

Joseph Sun
7/24/03 09:46:35 AM
PHARMACOLOGIST
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: (Division/Office) C. Sun/HFD-570			FROM: Craig M. Bertha/HFD-820	
DATE 4/21/03	IND NO.	NDA NO. 20-784	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 3/21/03 (assigned 4/1/03)
NAME OF DRUG Nasacor® HFA (triamcinolone acetonide) Nasal Aerosol		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE PDUFA date of 3/30/02
NAME OF FIRM: Aventis Pharmaceuticals, Inc. (US Agent is Quintiles)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> ORIGINAL NEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (Specify below)				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary): See attached sheet. cc: Orig. NDA # 20-784 HFD-570/CBertha HFD-570/Div. File HFD-570/GPoochikian HFD-570/LPei/VWhitehurst HFD-570/CJackson/SBarnes				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

Consult Request

Since much of the consult reviews for the drug product leachables and container closure component extractables were done in association with _____ and considering that the application has changed hands from RPR to Aventis, it is requested that the pharmacology/toxicology team evaluate or confirm the safety of the current leachables/extractables specifications for the Nasacort HFA Nasal Aerosol application of N20-784.

The leachables and extractables acceptance criteria are reproduced from the current and last amendment below. The leachables are defined as the compounds actually found in the drug product formulation during product shelf life. The extractables are compounds extracted by special methodology from the incoming drug product container closure components _____

_____ The extractables acceptance criteria can be viewed as the "worst-case" in terms of the potential amounts of these materials that may leach into the drug product during shelf-life.

The _____ acceptance criteria are given as the _____ The _____ extractables acceptance criteria are given as _____

The label claim number of actuations is 100 although there is a _____ overfill since each actuation delivers ~65 mg of formulation and the target fill weight is _____

It is also requested that the pharm./tox. team evaluate or confirm that there has been an evaluation _____

Note that for the following _____, the applicant has set the upper limits at the detection limit _____ of the method of _____, which equates to _____

Likewise, for the _____, the extraction method _____, and the applicant has set the upper limit on the _____, which is the detection limit defined with _____ With a _____ extraction volume this equates to _____ of each of these per canister at a maximum.

4 Page(s) Withheld

J Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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

/s/

Guiragos Poochikian
4/21/03 10:07:36 AM

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: NDA 20-784

Review number: 6

Sequence number/date/type of submission: November 30, 2001

Information to sponsor: Yes (X) No (), via the chemist

Sponsor and/or agent: Rhone-Poulenc Rorer, Collegeville, PA

Reviewer name: VE Whitehurst

Division name: Division of Pulmonary and Allergy Drug Products

HFD #: HFD 570

Review completion date: March 11, 2002

Drug:

Trade name: Nasacort HFA Nasal Aerosol

Generic name (list alphabetically): Triamcinolone acetonide

Relevant INDs/NDAs/DMFs: NDAs — 20-468, 19-798 and INDs 26,171,
— 43,841.

Drug class: Glucocorticosteroid

Indication: Seasonal and perennial rhinitis

Clinical formulation: Nasal spray

Route of administration: Intranasal

Proposed use: Adults: 440 µg/day (8.8 µg/kg for a 50 kg person)

Children: 220 µg/day

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

Executive Summary

I. Recommendations

A. Recommendation on Approvability: NA

B. Recommendation for Nonclinical Studies: NA

C. Recommendations on Labeling: NA

II. Summary of Nonclinical Findings: NA

A. Brief Overview of Nonclinical Findings: NA

B. Pharmacologic Activity: NA

C. Nonclinical Safety Issues Relevant to Clinical Use: NA

III. Administrative

A. Reviewer signature: V E Whitehurst

B. Supervisor signature: Concurrence - Robin A. Huff

Non-Concurrence - _____

(see memo attached)

C. cc: list:

Division file

HFD-570/SBarnes

HFD-570/RHuff

HFD-570/CBertha

HFD-570/VWhitehurst

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:..... 1

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IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Introduction: The purpose of this chemistry consult from Dr. Craig Bertha is to evaluate the safety of the proposed limit of not more than (NMT) _____ for the _____ impurity of triamcinolone acetonide (TAA) in Nasacort HFA Inhaler. The proposed limit for the _____ in the drug substance is also NMT _____

Conclusions: The following should be conveyed to the sponsor:

Because the _____ is a structural alert, either decrease the level of the impurity in the drug substance and the drug product to NMT _____ or qualify the impurity by conducting genotoxicity testing. In order to qualify the impurity, test the isolated aldehyde in the microbial mutation assay and either a mammalian chromosomal aberration assay or the mouse lymphoma tk assay.

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

/s/

Virgil Whitehurst
3/12/02 01:11:06 PM
PHARMACOLOGIST

Robin Huff
3/12/02 03:46:03 PM
PHARMACOLOGIST
I concur.

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division Of Pulmonary and Allergy Drug Products (HFD-570)

REVIEW INFORMATION:

Review No.: 4
Reviewer Name: Luqi Pei, Ph.D.
Key Words: Extractables, leachables, safety evaluation
Review Completion Date: January 27, 2000

APPLICATION INFORMATION:

NDA No: 20-784
Drug Name: Nasacort HFA-134a (Triamcinolone acetonide)
Sponsor: Rhone-Poulenc Rorer, Collegeville, PA

CHEMISTRY CONSULT INFORMATION:

Requested by: Dr. Vibhakar Shah
Date of Request: January 20, 2000
Content of the Request: Safety evaluation of leachables

Review Summary:

This review evaluates the safety of three leachables in Nasacort HFA[®]. They are _____ The review finds that the expected daily exposures of patients to the leachables _____/day, based on the proposed specifications) are 6 to 120 fold below their acceptable daily intakes established previously. The review concludes that the proposed specifications for the leachables are acceptable. The review, however, recommends tightening the specifications for the leachables to reflect the data as this would minimize patients' exposure to agents that lack any therapeutic effect but may present potential health hazards.

REVIEW:

This review is generated upon Dr. Vibhakar Shah's consult request dated January 20, 2000 (attached). Dr. Shah is the Chemistry Reviewer for the Nasacort HFA[®] NDA application. He specifically requested a safety evaluation of three leachables identified in the July 30, 1999 submission. These leachables are _____ The review is divided into 2 parts: exposure assessment and safety evaluation.

Exposure Assessment

The expected maximum daily exposure of these leachables in the Nasacort HFA[®] are _____ for _____

(Table 1). These exposure levels are based on the proposed specifications because they are higher than the actual data. For example, the proposed specification for _____ approximately 35% higher than the amount _____ detected at a shelf life of _____

Table 1. Leachables and Their Exposure Levels in Nasacort HFA®

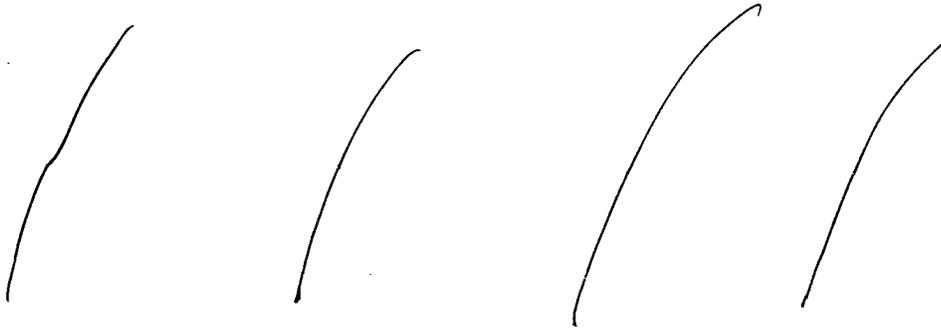
Safety Evaluation

The review evaluates the safety of these leachables by comparing their expected daily exposures with the accepted daily intake (ADI) established previously. The expected daily exposure is based on the proposed specifications. The review considers that once the exposures based on the proposed specifications are accepted, the exposure levels from the actual data are automatically accepted because the latter are always smaller than the former.

The review uses safety indexes to evaluate the safety of the leachables. The safety index refers to a ratio between the ADI and the expected human daily exposure. A safety index of greater than one indicates that the expected daily exposure is acceptable. The ADIs for these 3 leachables (_____ $\mu\text{g}/\text{kg}/\text{day}$) have been established previously (See Dr. L. Pei's Pharmacology and Toxicology Review _____). Table 2 (next page) presents the safety indexes for these leachables in Nasacort HFA®, based on the proposed specifications. Safety indexes for the three leachables are all greater than one (range 6 -120). Thus, the present levels of the leachables are acceptable.

However, tightening of the specifications for the leachables is recommended. This would minimize the exposure of patients to the leachables. These leachables not only lack any therapeutic effect, but also may present potential health hazards to the patients. Although their proposed specifications are acceptable, any exposure above the unavoidable amount is unwarranted. Thus, the sponsor should set the specifications for the 3 leachables to reflect the data. Similarly, the sponsor should tighten the specifications for other leachables and extractables not discussed in the review (e.g., _____).

Table 2. Safety Evaluation of Leachables in the Nasacort HFA®



Recommendation:

The proposed specifications are acceptable, but sponsor should be asked to tighten the specifications to reflect the data. This would ensure that patients are exposed to these leachables at levels as low as possible. Similarly, the sponsor should tighten the specifications for other leachables and extractables not discussed in the review.

Luqi Pei, D.V.M., Ph.D.
Pharmacologist/Toxicologist

Robin Huff, Ph.D.
Pharm/Tox Team Leader

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

Original, Review No. 2

NDA No. 20784
Serial No., Dates of Submission: October 24, 1996
Information to be conveyed to Sponsor: Yes (X), No ().
Reviewer: Luqi Pei, Ph.D. (HFD-570)
Date of Review Completed: December 3, 1997
Drug Name: *Generic Name:* Triamcinolone acetonide
Brand Name: Nasacort® HFA —
Sponsor: Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA.

Review:

RPR filed their original application for Nasacort®HFA-134a (NDA 20784) on December 17, 1996. Nasacort® HFA-134a is a multidose inhaler and indicated for seasonal and perennial rhinitis and allergy and intended to replace the Nasacort CFC product that is currently on the market. Its active ingredient is triamcinolone acetinode, a glucocorticosteroid. Pharmacology and toxicology review for original application was completed by Luqi Pei, Ph.D. on October 2, 1997. The original submission, however, lacked the extractable and leachable profiles of this new products. Upon the request by the Agency, RPR submitted a partial list of the extractable and leachable profiles in the submission of October 24, 1997. The sponsor is working to complete the rest of the study.

The sponsor has not submitted a complete profile of the extractables and leachables. Preliminary results indicated that 4 compounds, after a shelf life of _____ of the product, were present at appreciable amounts and warrant safety evaluation. They are _____ . Their expected consumption by the patient, the acceptable daily intake (ADI) and safety factors are summarized in Table 1.

With the exception of _____ the rest of the compounds were present in amounts well below the acceptable daily intake and do not cause safe concerns. The _____ concentration may be a safety concern because of its carcinogenic potential in the nasal cavity. Relevant information has been requested and the safety evaluation is in progress. Additional issues may also arise pending the completion of the extractable and leachable profiles by the sponsor. The final safety evaluation of the chemicals that may be present in the drug product should be conducted upon the submission of a complete profiles of the extractable and leachables.

Conclusion:

The sponsor should provide a complete profile of the extractables and leachables in the product. Final evaluation should be completed when data become available.

Draft letter to the sponsor:

The extractables and leachables chemical profile you submitted is incomplete. Provide a completed chemical profile and safety evaluation of the extractables and leachables that may be present in the drug product.


Luqi Pei, Ph.D. 12/3/97
Pharmacologist/Toxicologist

cc: HFD-570/Division File
HFD-570/ Pei/ Sheevers/ Himmel/Barnes


12/3/97

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

Original, Review No. 1

NDA No. 20784

Serial No., Dates of Submission: December 17, 1996

Information to be conveyed to Sponsor: Yes (X), No ().

Reviewer: Luqi Pei, Ph.D. (HFD-570)

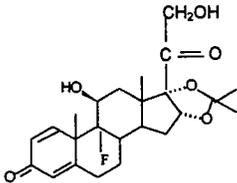
Date of Review Completed: October 2, 1997

Drug Name: *Generic Name:* Triamcinolone acetonide
Brand Name: Nasacort® HFA

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA.

Chemical Names: 9-fluoro-11 β , 16 α , 17, 21-tetrahydroxypregna-1,4-diene-11 β , 21-diol-3,20-dione cyclic 16, 17-acetal with acetone.

Structure:



Formula and Molecular Weight: C₂₄H₃₁FO₆, M.W. 434.5

Related INDs and NDAs:

NDA 20-468 Nasacort® AQ Nasal Spray
 NDA 19-798 Nasacort® Nasal Inhaler
 NDA 18-117 Azmacort® Oral Inhaler
 INDs: 26171, _____ 43,841, _____

Related DMFs: DMF _____

Class: Glucocorticosteroid

Indication: Seasonal and perennial rhinitis

Route of Administration: Nasal spray

Proposed Clinical Dose: Adult: 440 μ g/day, once a day. (8 actuations of 55 μ g/act.)
 Children (> 6 yr): 220 μ g/day

Previous Reviews: NDA 20-468 Dr. Whitehurst on September 25, 1995
 NDA 18-117 Dr. Chen on November 30, 1978

Formulation:

Ingredient	15 mg caniste	
	Quantity	Concentration (%)
Triamcinolone acetonide	15.0 mg	—
Dehydrated alcohol	—	—
HFA- 134a	—	—
Total	9.3	100

Documents reviewed in the NDA.**Pharmacology**

None.

Pharmacokinetics

Species	Route	Description	Report No.	Volume	Page
Rat	IV, IG, IN*	Disposition of ¹⁴ C-triamcinolone	DD-94-037	1.18	5-11-38
	PO, IV	Tissue distribution of ¹⁴ C-triamcinolone	DD-94-022	1.18	5-11-126
	IN	Whole body autoradiography	DD-94-136	1.19	5-12-1
		Metabolites in bile and urine	DD-94-141	1.19	5-12-97
		" LC/MS + ¹⁴ C-triamcinolone	DD-94-142	1.19	5-12-135
Dog	IV, PO	Disposition of ¹⁴ C-triamcinolone	DD-94-130	1.19	5-12-214
	"	"	DD-94-131	1.19	5-12-277
	"	Disposition supplement	DD-94-143	1.19	5-12-381

* = intranasal administration

Toxicology*

Species	Route	Duration	Formulation	Description	Report No.	Volume	Page
Dog	IN	1 day	MDI	Instillation	DS 93-060	1.9	5-2-1
(beagle)	IH	4 weeks	"	Oral inhalation	DS 92-055	1.13	5-6-1
"	IN	13 weeks	"	Instillation	DS 94-119	1.9	5-2-19
"	IH	1 year	"	Oral inhalation	DS 93-004	1.15	5-8-1
Rat	IH	13 weeks	"	Nose-only	DS 95-098	1.10	5-3-1

* With HFA-134a MDI formulation.

Background:

Triamcinolone is a glucocorticosteroid and the active ingredient of several the RPR products that are currently on the market: Azmacort® Oral Inhaler which is indicated for asthma, and Nasacort® (Nasal Spray and Nasal Inhaler) that are marketed for seasonal and perennial rhinitis and allergy. These products, approved between 1982 (Azmacort®) and 1994 (Nasacort® AQ), have been shown to be safe and effective clinically; however, they also release CFC, the excipient and an ozone depleting agent. With recent requirements to reduce the release of ozone-depleting agents into the environment, new and more environmentally friendly formulations are being developed. HFA-134a possesses less ozone-depleting properties. Several sponsors are developing HFA products to replace CFC containing products. RPR is developing Nasacort® HFA-134a to replace their existing CFC products.

REVIEW:**Pharmacokinetics:****Absorption:**

Pharmacokinetic parameters of ¹⁴C-triamcinolone after a single-dose administration was determined in Sprague-Dawley rats (IV, IG, and IN) and dogs (IV and PO). Triamcinolone was rapidly absorbed after oral and respiratory administration. Peak plasma concentration was reached approximately 30 minutes after dosing. Table 1 summarizes results in the males. The females data are quite similar and are not listed. Human data are listed for easy reference.

Table 1. PK of Single-dose TAA in, Male Rats and Dogs after IV, PO, IG and IN and Humans after PO Exposure

Route of administration	Rat			Dog		Human
	IV	IG	IN	IV	PO	PO
Dose (mg/kg)	1.0	1.0	0.065	0.8	0.8	0.016
N/time point/sex	3	3	3	4	4	6
C _{max} (ng/ml)	1846*	402	ND	1358*	58	1.6
T _{max} (hour)	-	0.8	ND	-	0.7	1.58
AUC ₀₋₄ (ng.hr/ml)	1308	677	32	660	115	8.61
AUC _{0-∞} (ng.hr/ml)	1489	689	-	662	121	9.24
Bioavailability (radioact.)	-	0.61 - 0.71	0.54-0.60		0.62	
(absolute)	-	0.46	0.38		0.2 - 0.3	0.11
Clearance (L/hr/kg)	0.67	0.69	-	1.2		
V _{dss}	1.67	1.43	-	1.4		
T _{1/2 α} (hr)	0.5	0.89	-	0.6	0.8	
β (hr)	7.3	2.2	-	3.0	3.5	6.7

* Earliest sampling point (5 and 2 minutes in rats and dogs, respectively).

ND = Not discernable from the plasma concentration. The limit of quantitation for TAA was 0.038 ng/ml when measured by radioimmunoassay (RIA).

Comment: PK data after oral administration (0.8 mg/kg) were quite variable in the dogs. Plasma peak concentration ranged from _____ ng/ml (Protocol DDP-94-130). The reason for this large variability was unknown.

Plasma triamcinolone concentration after repeated inhalation exposure was determined for a duration of up to one year in rats and dogs. Table 2 presents a summary of the plasma levels of respective studies. Although there was no gender difference in plasma concentration in dogs, female rats seemed to have higher plasma drug levels than the males. Also, the rats also seemed to have higher plasma drug levels than the dogs. Plasma drug levels did not vary as the exposure was prolonged.

Table 2. Plasma triamcinolone concentrations in repeated dose studies

Species	Route	Duration (wk)	Dose ($\mu\text{g}/\text{kg}/\text{day}$)	Mean AUC (ng/ml)	Study #
Rat, σ	Inhalation	13	5, 20, 80	5.5, 16.4, 49.7	DS 95-098
♀	"	"	"	11.6, 83, 157	"
Dog	Oral inhalation	4	40, 200, 400*	0.5, 1.4, 5.2	DS 92-055
	Nasal instill.	14	20, 44, 88	0.8, 1.0, 2.5	DS 94-119
	Oral inhalation	52	40, 200, 400*	0.6, 3.5, 31	DS 93-004

* Corrected doses. The sponsor reported these numbers as 80, 400, and 800 $\mu\text{g}/\text{kg}/\text{day}$, the amount of drug actually released from the mouth piece adapter. Snipes (Critical Rev. Toxicol, 1989;201:75-211) indicated that pulmonary deposition factor after oral inhalation was 50% in dogs.

Tissue distribution:

Tissue distribution of TAA was studied using radio-labeled isotopes in rats and dogs. Radioactivity derived from ^{14}C -TAA was widely distributed throughout the body regardless of the route of administration (IV, IN, PO). The highest concentrations were found in the liver, adrenal, kidney and blood. Distribution patterns were similar between males and females. Tissue TAA concentration declined over time. Table 3 presents tissue radioactivity after intranasal administration in male rats.

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Table 3. Mean Relative Density of ¹⁴C-TAA (nCi/mg wet tissue) in Male Rats after IN Dosing*

Tissue/organ	Time post treatment		
	0.25 hr	4.0 hr	24 hr
Brain	0.06	0.08	0.05
Spinal cord	0.05	0.08	0.05
Nasal cavity	6.82	2.22	0.05
Salivary gland	0.25	0.42	0.05
Thymus	0.15	0.37	0.05
Heart muscle	0.25	0.38	0.05
Blood	0.19	0.18	0.05
Lung	0.24	0.35	0.06
Liver	1.05	2.00	0.15
Stomach content	3.93	7.71	0.06
small intestine content	3.55	7.71	0.50
Large intestine content	0.07	1.76	2.05
Kidney	0.26	0.75	0.05
Adrenal gland	0.26	0.44	0.05
Skeletal muscle	0.10	0.16	0.05
Background	0.05	0.06	0.05

* n = 2/time point.

Metabolism:

Metabolism of triamcinolone has been reviewed by Dr. Conrad Chen previously (review of Nov. 30, 1978 in NDA 18-117). Those studies were conducted more than 20 years ago by the Lederle Laboratories. 6 β -hydroxy-TAA (24%) and 21-Carboxylic acid of 6 β -TAA (66%) were identified as the major metabolites in rats, rabbits, dogs and monkeys. Others identified later the presence of glucuronide conjugates. In this submission, RPR conducted 8 additional studies to update their knowledge of TAA metabolism using more advanced technology (radioisotopes, HPLC, and LC/MS). The RPR studies not only confirmed the previous observations, but also identified a few additional metabolites in the bile and urine in both rats and dogs. These metabolites, however, accounted for less than 10% of the total metabolites. A list of tentatively identified metabolites and their respective structure are presented in Table 4.

Table 4. Metabolites (%) of TAA in the Urine and Bile in Rats and Dogs

	Rat	Dog
Parent		< 17%
Metabolite	+	
6P-OH-TAA	+	6 - 40%
Triene-etianic acid	+	
21-Carboxylic acid of 6-OH-TAA	+	11 - 40%
Glucuronide conjugates of 6 β -OH-TAA	+	
Sulfate conjugate of 6 β -OH-TAA	+	
Disulfate of 21-Carboxylic, 6P-OH-TAA	+	+
# Unidentified		5

Elimination:

Feces is the major route of elimination for TAA in both rats and dogs. A small portion was eliminated through urine. Most of the drug was eliminated from the body 96 hours after administration (Table 5).

Table 5. Excretion of TAA in Urine and Feces*

	Rat		Dog	
	IV	PO	IV	PO
Feces	78.3	74.0	85.2	91.4
Urine	13.4	16.6	4.1	3.8
Total recovery#	92	91	90	96

* Mean in % of the total dose.

Include cage wash and cage wipes. Number in rats also included 0.23 % activity in the carcass.

Toxicology

1. 1-day intranasal toxicity study of MDI formulation in beagle dogs. (Report No. DS 94-060). Vol. 1.9, p 5-2-1. Submitted on 12/17/96.

Testing laboratory: Drug Safety Division, RPR
Study dates: 5/17/94 - 5/18/94, report date: 1/22/94
Study No. Same as Report No.
GLP: Yes
Batch formulation: Lot Nos. 15-22D- 1, MDI (Nasacort HFA- 134a)
Animal: Beagle dogs, 1/sex/dose
Dose: 0, 0.88 mg/dog

Two beagle dogs were given a single dose (0.44 mg/nostril) of Nasacort HFA-134a MDI to test acute irritancy/toxicity of the drug products. Two additional dogs were not treated and served as the control. All animals were sacrificed on the following day for microscopic examination of the nasal passage and the nasopharyngeal regions. No significant toxicological effects were observed.

2. A 4-week oral inhalation toxicity study of Nasacort® HFA-134a MDI with 2 weeks of recovery period in beagle dogs. (Report No. DS 92-055). Vol. 1. 13, p 1. Submitted on 12/17/96.

Testing laboratory: _____
Study dates: 6/26/92 - 8/4/92, report date: 9/18/93
Bio-Research No. 90597
GLP: Yes
Batch Iformulation: Lot Nos. 5 016/14- 1 B-2
Animal: Beagle dogs (3/sex/dose for the main study, 2/sex for recovery C, H)
Dose: 0, 40, 200, 400 µg/kg/day

* Corrected doses. The sponsor used a deposition efficiency of 100% in dogs and reported actual dosage as 80, 400, and 800 µg/kg/day for the low, mid and high dose groups, respectively. Snipes (Critical Rev. Toxicol, 1989;201:75-21 1) indicated that pulmonary deposition efficiency after oral inhalation was 50% in dogs. Therefore, the correct dose level should be 40, 200 and 400 µg/kg/day.

Method:

Beagle dogs (3/sex/dose) were exposed to triamcinolone at doses of 40, 200, 400 µg/kg/day by oral inhalation for 28 days. The daily doses were given in 2 sessions separated by 4 hours between sessions. The control groups included one air control and the other vehicle control. Most animals were sacrificed at the end of study. Two animals/sex in the vehicle control and high dose groups were allowed to recover for 2 weeks prior to the scheduled sacrifice. The following parameters were monitored during the experiment.

<i>Clinical signs:</i>	Daily
<i>Body weight:</i>	Weekly
<i>Food consumption:</i>	Daily, reported weekly
<i>Ophthalmology:</i>	Prior to treatment, week 4
<i>Clinical pathology:</i>	Prior to treatment, week 4
<i>EKG:</i>	Start of the treatment, week 4
<i>Plasma drug level:</i>	Days 1, 28, and 42
<i>Pathology:</i>	
<i>Organ weights:</i>	Adrenals, brain, heart, kidneys, liver, lungs, ovaries, testes, pituitary, prostate/uterus, salivary glands, spleen, thymus, thyroid and parathyroid
<i>Necropsy:</i>	Preterminal and terminal sacrifice
<i>Histopathology:</i>	Nasal cavity (3 levels) and nasopharynx

Results:

Mortality: None.

Clinical signs: No treatment-related effects were found.

Body weight: A dose-related loss in body weight was seen in all treated females and the mid and high dose males (Table 6).

Table 6. Body weight gain and Food Consumption

Dose ($\mu\text{g}/\text{kg}/\text{day}$)	0 (air)	0 (vehicle)	40	200	400
Body weight gain (kg)					
Male	0.30	0.44	-0.13	-0.36	-0.80*
Female	0.10	0.12	0.40	-0.20	-0.44
Food consumption (%)					
Male	-	↓ 10%	↓ 6 %	↓ 16 %	↓ 34 %*
Female	-	↓ 6%	↑ 4 %	↓ 23 %	↓ 33 %

* No statistical significance was achieved due to the high variability during the experiment.

Food consumption: A dose-related decrease in food consumption was seen in both sexes (Table 6).

Ophthalmology: No treatment-related effects were observed.

EKG: No treatment-related effects were observed.

Clinical pathology: No remarkable changes in hematology, blood chemistry, and urinalysis were noticed.

Organ weights: Noticeable and/or relevant changes in organ weights are summarized in Table 7. The high dose animals showed smaller adrenal glands, thymus and spleen, and large liver. Small thymus was evident even in the low dose females. Dose-related changes in liver (increase) and spleen (decrease) weights were apparent, but none reached statistical significance. All changes appeared to return to normal after the recovery period.

Table 7. Mean Organ Weights (n = 3) in a 4-Week Inhalation Toxicity Study of Triamcinolone

Dose ($\mu\text{g}/\text{kg}/\text{day}$)	Male					Female				
	0	0	40	200	400	0	0	40	200	400
Body weight, terminal (g)	8.9	9.1	9.2	8.2	8.4	7.4	7.2	7.3	6.6	6.8
Adrenal, abs. (g)	0.92	0.99	0.87	0.60	0.56	0.68	0.91	0.77	0.59*	0.45*
rel. @ x 100	1.1	1.2	1.1	0.7*	0.7*	0.9	1.3*	1.0	0.8*	0.6*
Brain, abs. (g)	80.2	80.9	78.0	80.7	76.2	77.2	69.1	73.7	71.2	75.4
Liver, abs. (g)	319	334	335	340	384	246	22	259	239	295
rel.	3.99	4.15	4.29	4.22	5.05	3.18	3.24	3.54	3.36	3.89
Lung, abs. (g)	98.5	93.7	95.3	82.8	90.8	78.7	66.9	74.6	65.5	62.4
rel.	1.23	1.16	1.23	1.003	1.19	1.02	0.98	1.02	0.92	0.83
Spleen, abs. (g)	61.2	36.6	33.2	36.3	28.7	44.6	33.5	33.9	48.6	28.0
rel.	0.76	0.45	0.43	0.45	0.38	0.59	0.50	0.46	0.68	0.38
Thymus, abs. (g)	7.38	7.48	3.5*	2.8*	1.50*	5.9	4.0	5.5	1.4*	1.4*
rel. @ x 100	9.2	9.3	4.6*	3.4*	2.0*	8.0	5.8	7.7	2.0*	1.9*

@ relative to body weight, g/g., * P < 0.05.

Pathology:

Necropsy: Noticeable gross pathological observations included small thymus in the mid and high dose animals (0/6-C, 0/6-LD, 1/6-MD, 4/6-HD).

Histopathology: Atrophy of the adrenal and lymphoid tissues was evident in the mid and high dose groups (Table 8). Thymus atrophy was seen in all treated groups.

Table 8. Microscopic findings in a 4-Week Inhalation Toxicity Study of Triamcinolone (n = 3/dose)

Dose ($\mu\text{g}/\text{kg}/\text{day}$)	Male					Female				
	0	0	40	200	400	0	0	40	200	400
Adrenal atrophy	0	0	0	3	3	0	0	0	2	3
Bone marrow, T stromal fat	0	1	0	3	3	1	0	0	2	3
Bronchial inflam., acute	0	0	0	0	2	0	0	0	0	0
Lymphoid atrophy, ileum	0	0	0	2	3	0	0	0	3	3
nasal	0	0	0	0	3	0	0	0	0	0
tracheobr	0	0	0	0	1	0	0	0	0	3
Liver, T glycogen	0	0	0	3	3	1	1	1	1	3
Thymus atrophy	0	0	3	3	3	0	0	0	3	3

Recovery animals: Two animals per sex in the vehicle control and high dose group were allowed to recover for 2 weeks prior to sacrifice. Few microscopic changes remained in the treated group: vacuolization of adrenal cortex, atrophy of the lymphoid tissues (ileum), increased stromal fat in bone marrow, depletion of lymphocytes in the spleen in both sex. Thymus atrophy and cell infiltration in the liver were seen in males only.

Plasma drug levels (Days 1 and 28): Plasma triamcinolone levels for the low, mid and high dose groups were 0.46, 1.35, and 5.23 ng/ml when determined by RIA assay. The low limit of quantitation was 0.25 ng/ml. There was no apparent gender differences and bioaccumulation over time.

Conclusion: Oral inhalation exposure of triamcinolone at 40, 200, and 400 $\mu\text{g}/\text{kg}/\text{day}$ produced dose-dependent and characteristic changes of inhaled steroids: decreases in body weight, and in the weights of thymus and adrenals. The decreases in the weights of thymus and adrenal glands was accompanied by tissue atrophy upon microscopic examinations. These changes were still evident after a recovery period of 2 weeks. No NOAEL value was established.

3. A 3-month inhalation (nose-only) toxicity study of MDI formulation in Sprague-Dawley albino rats. (DS 95-098). Vol. 1. 10, p 4-3-1. Submitted on 12/17/96.

Testing laboratory: _____
 Study dates: 10/19/95, report date: 2/6/96
 Bio-research No. 91178
 GLP: Yes
 Batch Information: _____ Lot Nos. 23-3A-2/3
 Animal: Sprague-Dawley albino rats CD®(SD)BR
 Dose: 0 (air), 0 (vehicle), 5*, 21, and 87 µg/kg/day

*The sponsor reported as 0.005, 0.02, 0.08 mg/kg/day.

Methods:

Sprague-Dawley rats (10/sex/dose, age of 6 - 7 weeks) were exposed by nose-only inhalation to triamcinolone for 13 weeks. The respective dose levels for the low, mid and high dose groups were 5, 20 and 80 µg/kg/day for total body exposure and 1.2, 4.3 and 18 µg/kg/day for pulmonary exposure. Chamber concentrations of triamcinolone were 0.5, 1.8, and 7.5 µg/L for the low, mid and high dose groups, respectively. The daily exposure duration was 30 minutes. The control groups included one air control and one vehicle control. The estimated MMAD was _____ µm. Animals were sacrificed at the end of treatment for necropsy and histological examinations.

Comment: Determination of pulmonary exposure dose levels (Table 9) _____

Table 9. Estimated exposure levels of triamcinolone in the 13-week intranasal toxicity study in rats

Group	Chamber concentration# (µg/L)	Total body exposure (µg/kg)*	Pulmonary exposure (µg/kg)**
Low dose	0.5	5	1.2
Mid dose	1.8	20	4.3
High dose	7.5	80	18.0

* Based on a deposition factor of 0.7 (Snipes, *Critical Rev Toxicol*, 1989;20:1 75 - 21 1).

** Based a pulmonary deposition factor of 0.1, and the minute volume of 0.8 L/min/kg (Reference same as the above).

Exposure (µg/kg) = chamber concentration x exposure duration x minute volume/kg x deposition factor

The following parameters were monitored during the experiment.

<i>Clinical signs:</i>	Daily
<i>Body weight:</i>	Weekly
<i>Food consumption:</i>	Daily, reported weekly
<i>Ophthalmology:</i>	Prior to treatment, weeks 6 and 13
<i>Clinical pathology:</i>	Prior to treatment, weeks 6 & 13
<i>EKG:</i>	Start of the treatment, weeks 6 and 13
<i>Plasma drug level:</i>	Day 1 and 85
<i>Pathology:</i>	
<i>Organ weights:</i>	All major organs
<i>Necropsy:</i>	Preterminal and terminal sacrifice
<i>Histopathology:</i>	A complete panel

Results:

Mortality: One high dose female (No. 5509) was euthanized on day 67 (week 10) because of poor and deteriorating condition. This animal had a damaged eye subsequent to the bleeding procedure performed on week 6. This mortality did not appear to be treatment-related.

Comment: The immunosuppression nature of the TAA, the severe toxic responses of females (loss of weight etc.), and the occurrence of euthanasia long after blood sampling strongly suggest that the death be treatment-related, although other findings indicated that the death was not treatment-related. This animal appeared to be healthy in week 6 and its clinical pathological parameters were normal. It gained the second-most body weight in its group prior to its sacrifice. Necropsy revealed discoloration of the right eye, area dark of mandibular lymph node, small thymus and loss of bronchial lymph node. Microscopic examination revealed mild immunosuppression: atrophy of thymus, spleen and lymph nodes of various locations.

Clinical signs: Dose-related increases in the incidences of thinning of hair coat were observed, especially in the females. Changes were mostly present in the lumbar, muzzle and sacral regions.

Body weight: TAA caused dose-dependent decreases in body weight gain in all treated groups (Table 10). The low dose males, which showed the least response, had a 28% decrease in body weight gain on day 91. The high dose males showed an 87% decrease in body weight gain, compared to the control. The females gave a stronger response; the high dose females actually lost body weight (9%) over the course of treatment.

Table 10. Body weight in a 13-week intranasal toxicity study of triamcinolone

Sex	Day	Dose ($\mu\text{g}/\text{kg}/\text{dav}$)				
		0 (air)	0 (vehicle)	5	20	80
Male	1	240	244	246	239	243
	29	361	370	336*	283*	255*
	57	425	442	392*	342*	271*
	91	468	479	411*	317*	274*
Female	1	177	178	176	179	182
	29	228	223	198*	177*	173*
	57	246	239	211*	186*	174*
	91	261	256	210*	189*	162*

$P < 0.05$.

Food consumption: Dose-related decreases in food consumption was observed in the mid and high dose groups. The high dose groups showed about 20% decrease in food consumption on day 91. The low animals showed occasionally decrease in food consumption.

Ophthalmology: No treatment-related effects were observed.

Clinical pathology: Table 11 lists changes in hematology, blood chemistry and urinalysis of the study at weeks 13 or 14. Most changes also occurred at week 6.

Table 11. Clinical Pathology Results in a 13-week Inhalation Toxicity study of triamcinolone

Dose (4/dog)	Male					Female				
	0	0	5	20	80	0	0	5	20	80
Hematology										
WBC (x 10 ⁶)	9.4	9.1	7.4	5.0*	4.8*	6.4	6.2	3.6*	2.1 *	3.0*
Neutrophils, seg	20.4	19.2	21.8	58.0*	74.1 *	16.5	16.8	38.1*	66.2*	82.1*
Lymphocytes (x 10 ⁶)	5.1	4.5	3.8	1.4*	0.9*	3.0	2.4	1.6	0.7*	0.3*
Blood chemistry										
AST (U/L)	157	110*	121	175*	169*	125	129	416*	533*	317*
Bilirubin, total (mg/dl)	0.15	0.14	0.15	0.14	0.22*	0.18	0.21	0.21	0.22	0.24*
ALP (U/L)	74.3	77.2	95.1	109*	122*	44.1	41.8	52.1	73.5	88.8*
Phosphorus (mg/dl)	7.1	7.0	7.2	8.6*	8.6*	7.1	7.4	7.8	8.6	9.2*
Total Protein (g/dl)	6.1	6.1	6.1	6.3	6.8*	6.6	6.8	6.8	6.6	6.2*
BUN (mg/dl)	12.8	12.2	12.7	12.7	14.6*	0.98	1.01	1.03	1.06*	1.08*
Urinalysis, wk 13										
Osmolarity (mOsm/kg)	1034	1368	890	774	734	997	950	668	833	528*
K (mEq/L)	146	181	120	70*	64*	110	112	62*	66*	54*
Creatinine (mg/dl)	121	157	106	94	66.7	77.7	77.1	42.6*	59.8	28.4*

* $P < 0.01$.

Organ weights: Changes in organ weights are summarized in Table 12. Decreases in adrenal glands and thymus weights and increase in relative liver and lung weights was seen in the mid and high dose males and all females. The changes were more pronounced in the high dose group.

Table 12. Mean Organ Weights in a 13-Week Triamcinolone Inhalation Toxicity Study

Dose ($\mu\text{g}/\text{kg}/\text{day}$)		Male			Female						
		0	0	5	20	80	0	0	5	20	80
Body weight, terminal (g)		438	449	380*	309*	247*	245	233	185*	164*	140*
Adrenal,	abs. (mg)	45	48	42	27*	16*	51	54	38*	21*	14*
	rel. (@)	10	11	11	9	6*	22	23	21	12*	10*
Brain,	abs. (mg)	2137	2113	2092	2095	2112	1937	1933	1911	2018	1946
	rel.	491	474	552#	685*	861*	832	833	1037*	1243*	1396*
Gonads,	rel.	396	377	436	525*	646*	36	31	44*	51*	63*
Heart,	abs. (g)	1.61	1.60	1.51	1.43#	1.31*	1.00	1.05	0.98	0.98	0.97
	rel.	319	342	359	423*	502*	429	254	531*	603*	694*
Kidneys,	abs. (g)	2.70	2.85	2.65	2.47*	2.27*	1.69	1.66	1.63	1.60	1.55
	rel.	616	636	699#	803*	921*	720	714	886*	983*	1109*
Liver,	abs. (g)	11.3	11.4	9.7*	8.8*	7.4*	6.22	6.34	5.55*	5.55*	5.20*
	rel.	2574	2530	2550	2857#	3024*	2649	2726	2999*	3403*	3708*
Lung,	abs. (g)	1.39	1.53	1.36	1.30#	1.23*	1.10	1.12	1.06	1.07	1.07
	rel.	319	342	359	423*	502*	469	482	575*	661*	765*
Salivary gland, abs. (mg)		563	560	534	294#	453*	347	335	321	341	289*
	rel.	129	125	141	160*	183*	150	144	174#	209*	207*
Spleen,	abs. (mg)	783	694	610*	455*	365*	509	525	406*	323*	268*
	rel.	179	155	161	147#	146#	220	226	220	197	190
Thymus,	abs. (mg)	208	186	119	42*	24*	125	140	45	17*	17*
	rel.	49	42	31#	13*	10*	53	60	24*	10*	12*
Thyroid/parathyroid, (mg)		21	23	20	17*	15*	16	16	14	12*	12*
	rel.	5	5	5	5	6	7	7	8	7	8
Uterus,	abs. (mg)	-	-	-	-	-	443	637*	384*	384*	319*
	rel.	-	-	-	-	191	269	211	237	227	

* $P < 0.01$, # $p < 0.05$. @ = $\text{mg}/\text{g} \times 100$.

Pathology:

Necropsy: Table 13 presents significant gross pathological observations. Findings include dose-related increases in the incidences of small adrenal, thymus, lymph nodes and spleen.

Table 13. Gross necropsy observations in a 13-Week Inhalation Toxicity Study of Triamcinolone

Dose ($\mu\text{g}/\text{kg}/\text{day}$)		Male			Female						
		0	0	5	20	80	0	0	5	20	80
N/dose		10	10	10	10	10	10	10	10	10	10
Adrenal, small		0	0	0	6	9	0	0	2	9	9
Lung, area pale		0	0	0	0	1	0	0	1	4	6
Lymph node, bronchial, not found		0	0	0	1	1	0	0	1	2	4
Skin, thin hair coat		1	0	2	7	7	4	4	10	10	9
Spleen, small		0	0	0	0	3	0	0	0	0	3
Thymus, small		1	0	2	9	10	1	1	9	10	10

Histopathology: Table 14 presents microscopic changes in the study. Typical steroid effects were apparent in all groups, except the low dose males. These changes included atrophy of adrenal gland, thymus, spleen, lymph nodes, and the skin, and accumulation of adipose tissues in the bone marrow.

Table 14. Microscopic observations in a 13-Week Inhalation Toxicity Study of Triamcinolone

Dose ($\mu\text{g}/\text{gk}/\text{day}$)	Male						Female			
	0	0	5	20	80	0	0	5	20	80
N/dose	10	10	10	10	10	10	10	10	10	10
Adrenal atrophy	0	0	0	3	8	0	0	1	7	8
Bone, trabecular thinning	0	0	0		7	0	0	0	0	7
fusion, trabec + spong.	0	0	1	4	10	0	0	0	0	0
Harderian GL inflamm. chron	0	0	0	0	3	0	0	0	0	3
Liver, kupffer cell pigment	0	0	0	0	0	1	0	1	2	6
focal necrosis, central	0	0	0	0	0	0	0	1	0	1
Lymph node atrophy, lung	1	1	2	4	10	2	0	5	9	10
nasal vavity	1	2	2	8	10	0	0	7	10	10
Nasal cavity I, II, III, inflarn.	2	1	0	0	1	0	0	0	0	1
Marrow, T adipose tissue,	1	0	1	8	9	2	3	8	8	10
Mammary, hyperplasia	0	0	0	0	0	2	4	6	8	6/7
Skin atrophy	0	1	0/2	4/7	7/8	2	2	5	7	9/9
Spleen lymphoid atrophy	0	0	0	6	9	0	0	3	6	9
Thymus atrophy	1	0	2	9	10	2	2	8	9	10
Vagina mucification	-	-	-	-	-	3	3	4	6	7

Plasma drug levels (from satellite animals on days 1 and week 13): Table 15 lists the mean AUC and Cmax values of triamcinolone. The females possessed higher (2 - 4 x) plasma drug levels than the males. The limit of quantitation was 0.025 nmol/l.

Table 15. Plasma Triamcinolone Levels in a 13-week Inhalation Toxicity Study in Rats*

Dose ($\mu\text{g}/\text{kg}$)	AUC _{0-∞} (ng.h/ml)			Cmax (ng/ml)		
	5	20	80	5	20	80
Male	37.3	65.1	1284	6.7	16.1	45.7
Female	97.6	307	1284	14.4	63.8	213

* Results on Day 1. Values from week 13 are similar. Data were extracted from page 48 of the

Conclusion: Inhalation exposure of triamcinolone for 13 weeks produced typical glucocorticosteroid responses in rats: decreases in body weight gain, clinical pathologic changes and immunosuppression. Although females seemed to be more sensitive, pharmacokinetic analysis indicated that they possessed higher plasma drug levels than the males. No NOEL was clearly established.

4. 3-month intranasal toxicity study of MDI formulation in beagle dogs. Report and Study No. DS 94-119. Vol. 1.9, p 5-2-190. Submitted on 12/17/96.

<i>Testing laboratory:</i>	Drug Safety Division, RPR
<i>Study dates:</i>	11/2/94 - 3/10/95, report date: 8/9/95
<i>GLP:</i>	Yes
<i>Batch formulation:</i>	Lot Nos. 5029/15-25A- 1, MDI (Nasacort HFA- 134a)
<i>Animal:</i>	Beagle dogs, 3-4/sex/dose, 2/dose/sex for recovery groups (C & H)
<i>Dose:</i>	0, 0.22, 0.44, 0.88 mg/dog/day

Method:

Fours groups of beagle dogs (3 - 6/sex/dose) were exposed to triamcinolone (0.0, 0.22, 0.44 and 0.88 mg/dog) once a day by intranasal instillation for 91 days. These dogs were 5 - 6 months old at the beginning of the treatment and weighed 7.1 - 9.7 kilograms. Most animals (3 - 4/dose/sex) were terminated on day 91 and histological and pathological examinations were performed. The rest (2 dogs/sex for the control and high dose groups) were allowed to recover for 4 weeks prior to the scheduled sacrifice. The following parameters were monitored during the experiment.

<i>Clinical signs:</i>	Daily
<i>Body weight:</i>	Weekly
<i>Food consumption:</i>	Daily, reported weekly
<i>Ophthalmology:</i>	Prior to treatment, weeks 6 and 13
<i>Clinical pathology:</i>	Prior to treatment, days 36, 85 and 120
<i>EKG:</i>	Start of the treatment, weeks 6 and 13
<i>Plasma drug level:</i>	Day 1, 28 and 91
<i>Pathology:</i>	
<i>Organ weights:</i>	Adrenals*, brain, heart, kidneys*, liver, lungs, ovaries*, testes*, pituitary, prostate/uterus, salivary glands*, spleen, thymus, thyroid and parathyroids * also in the recovery animals
<i>Necropsy:</i>	Preterminal and terminal sacrifice
<i>Histopathology:</i>	Nasal cavity (3 levels) and nasopharynx

Results:

Mortality: None.

Clinical signs: No treatment-related effects were found.

Body weight: The high dose females showed a slight decrease in body weight (7%) on day 91. All of the treated males showed a slight decrease in body weight throughout the experiment but a dose-response relationship was lacking.

Food consumption: No treatment-related effects were observed.

Ophthalmology: No treatment-related effects were observed.

EKG: No treatment-related effects were observed.

Clinical Pathology: No apparent treatment-related effects were observed in hematology, blood chemistry, and urinalysis.

Organ weights: Table 16 summarizes group means of the absolute and relative organ weights. Decreases in the weights of adrenal glands and thymus were apparent, especially in the high dose group. The adrenal weight did not returned to normal after a recovery period of 4 weeks. The high dose males (n = 2) possessed an adrenal gland that was only a half of the control animals in weight. Weights of thymus and liver apparently returned to normal after the recovery period.

Table 16. Organ weights in a 13-week intranasal toxicity study of triamcinolone

Dose (mg/dog)		Male			Female				
		0	0.22	0.44	0.88	0	0.22	0.44	0.88
	Body weight (kg)	11.1	9.85	9.28	10.2	9.45	8.67	8.35	8.69
Adrenal:	Absolute (g)	1.35	1.10	0.96	0.64*	1.33	1.04	1.02	0.56*
	Relative (% x 100)	1.31	1.24	1.10	0.70*	1.63	1.30	1.30	0.68*
Gonads:	Absolute (g)	15.5	13.7	14.7	12.1	0.83	1.44	0.75	0.78
	Relative(% x 100)	0.15	0.15	0.17	0.13	0.99	1.77*	0.93	0.95
Heart:	Absolute (g)	93.3	81.1	79.6	80.0	85.4	79.1	83.1	76.0
	Relative(% x 10)	0.90	0.90	0.92	0.85	1.02	0.99	1.06	0.94
Liver:	Absolute (g)	306	297	334	361	271	302	278	310
	Relative (% x 10)	2.97	3.33	3.87*	3.81	3.28	3.76	3.55	3.82
Lung/bronch.:	Absolute (g)	104	79.2	79.3	79.0	83.3	72.3	74.4	72.9
	Relative (% x 10)	1.01	0.89	0.91	0.86	1.00	0.90	0.95	0.91
Pituitary:	Absolute (g)	0.08	0.05	0.10	0.06	0.06	0.12	0.11	0.10
	Relative (% x 1000)	0.08	0.06	0.12	0.01	0.07	0.15	0.14	0.13
Spleen:	Absolute (g)	55.4	61.6	24.0	35.9	38.9	28.8	64.7	56.1
	Relative (% x 10)	0.54	0.65	0.28	0.37	0.49	0.36	0.84	0.69
Thymus:	Absolute (g)	11.0	5.13*	4.44*	3.66*	6.29	3.19	2.62	3.29
	Relative (% x 1 00)	1.06	0.55*	0.51*	0.38*	0.74	0.40	0.32	0.39
Thyroids:	Absolute (g)	0.82	1.05*	1.23 *	0.94	1.05	0.80	1.10	1.02
	Relative (% x 1000)	0.79	1.18	1.43 *	1.00	1.26	0.99	1.41	1.24

* P < 0.05. (n = 3 - 4)

Pathology:

Necropsy: Significant gross pathological observations are presented in Table 17. Small adrenals and thymus were seen in all treated groups. Skin and lymph node discoloration were seen in the high dose females (2/4).

Table 17. Gross necropsy observations (incidences) in a 13-week intranasal toxicity study of triamcinolone

Dose (mg/dog)	<u>Male</u>				<u>Female</u>			
	0	0.22	0.44	0.88	0	0.22	0.44	0.88
Adrenal, small	0/4	1/3	1/3	4/4	0/4	0/3	1/3	2/4
Thymus, small	0/4	0/3	1/3	3/4	0/4	1/3	3/3	2/4
Lymph node discoloration*	0/4	0/3	0/3	0/4	0/4	0/3	0/3	2/4
Skin discoloration	0/4	0/3	0/3	0/4	0/4	0/3	0/3	2/4

* sublumbar lymph node.

Histopathology: Only nasal cavity and the nasopharyngeal regions were examined microscopically in this study. Both locations showed atrophy of the lymphoid tissues (Table 18).

Table 18. Microscopic observations (incidences) in a 13-week intranasal toxicity study of triamcinolone

Dose (mg/dog)	<u>Male</u>				<u>Female</u>			
	0	0.22	0.44	0.88	0	0.22	0.44	0.88
Nasal cavity								
Lymphoid tissue atrophy								
Section 11	0/4	0/3	3/3	4/4	0/4	0/3	2/3	4/4
Nasopharynx								
Lymphoid tissue atrophy	0/4	0/3	3/3	4/4	0/4	0/3	2/3	4/4

All of the parameters except the adrenal weights in the high dose males returned to normal after a recovery period of 4 weeks. Changes in other organs were unknown.

Plasma drug levels (Day 1, 28 and 91): Plasma triamcinolone levels one hour post dosing on day 1 are shown in Table 19. There was no apparent gender difference, nor drug accumulation over time.

Table 19. Plasma Triamcinolone Levels in a 13-week Intranasal Toxicity Study in Dogs

<u>Dose (μg/dog) *</u>	<u>C_{max} (ng/mL)</u>		
	<u>220</u>	<u>440</u>	<u>880</u>
Mean	0.76	1.01	2.53
Range			

Conclusion: Intranasal exposure of triamcinolone for 13 weeks produced a typical glucocorticosteroid responses in dogs: decrease in body weight gain and atrophy of the lymphoid tissues in the upper respiratory tract (microscopic examinations of other tissues were not conducted). No NOEL was clearly established.

5. 1-year inhalation toxicity study of MDI formulation in juvenile beagle dogs. Report No. DS 93-004. Vol. 1.15, p 1. Submitted on 12/17/96.

Testing laboratory: _____
 Study number: 90743
 Study dates: 1/28/93 - 3/4/94, report date: 10/27/95
 GLP: Yes
 Batch /formulation: Lot Nos. 5016/14-1C-1 & 5014/14-1E-1, MDI
 Animal: Beagle dogs, 4 - 6/sex/dose
 Dose: 0 (air), 0 (vehicle), 0.08, 0.4, 0.8 mg/kg

* Corrected doses. The sponsor use a deposition efficiency of 100% in dogs and reported actual dosage as 80, 400, and 800 µg/kg/day for the low, mid and high dose groups, respectively. Snipes (Critical Rev. Toxicol, 1989;201:75-21 1) indicated that pulmonary deposition factor after oral inhalation was 50% in dogs. The correct dose level should be 40, 200 and 400 µg/kg/day.

Methods:

Juvenile beagle dogs (4 - 6/sex/dose, age of 3.5 - 4 months) were dosed with triamcinolone by oral inhalation exposure for 52 weeks at 0.04, 0.2 and 0.4 mg/kg (respiratory tract and lung deposition dose). These doses were given as 0.02, 0.1, and 0.2 mg/kg twice daily with an interval of 4 hours apart. Two additional groups (4 - 6/sex/dose) received either air (sham) or vehicle alone as the controls. The estimated MMAD was _____ µm. An interim analysis (2/sex for the vehicle control and all high dose animals) was conducted on week 37. The interim analysis was carried out due to the high mortality and the declining general condition of the high dose group. The remaining animals were sacrificed at the end of treatment for necropsy and histological examinations. The following parameters were monitored during the experiment.

<i>Clinical signs:</i>	Daily
<i>Body weight:</i>	Weekly
<i>Food consumption:</i>	Daily, reported weekly
<i>Ophthalmology:</i>	Start of the treatment, weeks 13, 26, 38, 43, 52
<i>Clinical pathology:</i>	Prior to treatment, weeks 13, 26, 37, 52 of Hematology, blood chemistry and urinalysis.
<i>EKG:</i>	Start of the treatment, weeks 13, 26, 37/38, 52
<i>Plasma drug level:</i>	Day 1, weeks 4, 38, 52 after 2 nd session (Pre-Rx and 1 hour)
<i>Pathology:</i>	
<i>Organ weights:</i>	Adrenals, brain, heart, kidneys, liver, lungs, ovaries, testes, pituitary, prostate/uterus, salivary glands, spleen, thymus, thyroid and parathyroids
<i>Necropsy:</i>	Preterminal and terminal sacrifice
<i>Histopathology:</i>	Adrenals, aorta, bone and marrow, brain, bronchi, cecum, colon, duodenum, epididymides, esophagus, eyes, ileum, jejunum, heart, kidneys, lacrimal glands, larynx, liver, lungs, lymph nodes, mammary glands, nasal cavity and sinuses, optic nerves, ovaries, pancreas, pharynx, pituitary, prostate, rectum, salivary glands, skeletal muscle, spinal cord, stomach, spleen, testes, treacha (interim analysis), thymus, thyroid and parathyroids, urinary bladder, uterus, vagina

Tracheal measurement: Height, wall thickness, circumference and diameters of tracheal rings (2, 10, 20, 30) at terminal sacrifice

Notes:

1. The vehicle control group was mis-dosed with triamcinolone for one session on day 129. The amount of the drug received by animals were unknown.
2. The sponsor submitted very limited dosimetry data for this study. The sponsor has been asked to provide a more detailed description of the dosimetry. This included stability data, dose uniformity and dose estimations. This review assumes that the dosimetry claimed by the sponsor was appropriate. The revision of this review may be necessary should the actual data be significantly different from the claimed data.

Results:

Mortality: Several mortalities occurred during the treatment. Distribution and incidences of the mortality and the pre-terminal sacrifices are shown in Table 20:

Table 20. Mortality in the 52 week inhalation toxicity study of triamcinolone in juvenile dogs

Groups	Male					Female				
	1	2	3	4	5	1	2	3	4	5
Dose(mg/kg/day)	0	0	0.04	0.2	0.4	0	0	0.04	0.2	0.4
<u>Animals #</u>	<u>4</u>	<u>6</u>	<u>4</u>	<u>4</u>	<u>6</u>	<u>4</u>	<u>6</u>	<u>4</u>	<u>4</u>	<u>6</u>
Day 90				1 ^a						
Day 243										1 ^b
Day 257										1 ^c
Day 265					6 ^d					4 ^d
Day 275				1 ^d						
Total				2/4	6/6					6/6

a = Died of anesthesia following surgery for hernia, weakness, and intermittent tremors.

b = Euthanized after reduced activity and tremors

c = Found dead, having demodex.

d = Preterminal sacrifice due to humane reasons

Clinical signs (daily): No individual data were submitted. According to the summary report, no apparently treatment-related effects were observed. However, hernia was observed in the mid and high dose groups (1/8-MD, 3/12-HD).

Body weight (weekly): Table 21 and Fig. 1 & 2 present changes in group mean body weight during the course of the study. Difference in the absolute body weight in this study are less indicative of toxicity because both the male and female high dose groups had higher body weight (10%) at the beginning of the study. This large variation in body weight may undermine a clear-dose relationship in terms of body weight and organ weights.

Table 21. Body weight in dogs at the start of the triamcinolone treatment

Group	1	2	3	4	5
Dose (mg/kg)	0 (sham)	0 (vehicle)	0.04	0.2	0.4
Male (kg)					
Beginning	5.4	5.27	5.1	5.15	5.62
Terminal	11.6	10.8	9.6	10.6	9.4*
Female (kg)					
Start	4.05	4.35	4.15	3.9	4.3
Terminal	7.3	8.4	6.9	5.8	6.1*

* Week 37.

The relative body weight gain during the experiment as the percentage of the body weight at the beginning of the treatment is shown in Fig 2. The high dose males and all treated females showed decreases in body weight gain throughout treatment.

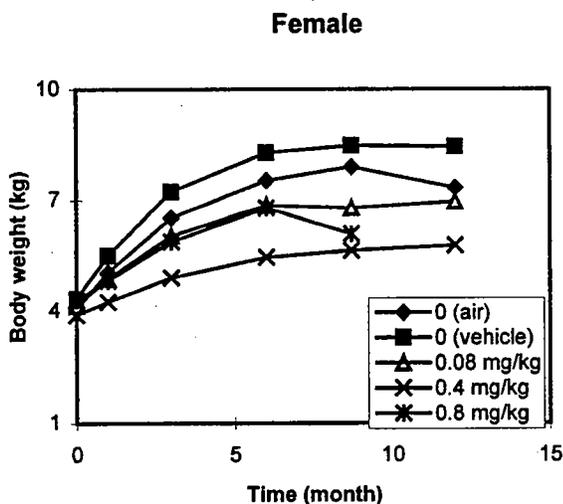


Fig. 1. Body weight changes in the females. Note that the mid dose group started out with a low body weight and it lasted throughout the experiment. The corrected doses should be 0.04, 0.2 and 0.4 mg/kg/day for the low, mid and high dose groups, respectively.

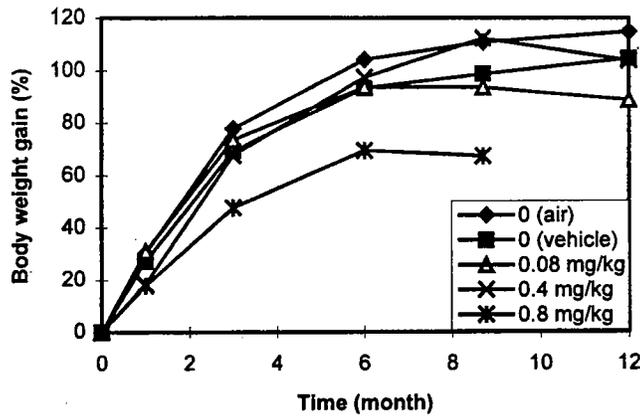


Figure 2a. Relative body weight gain (%) in males.

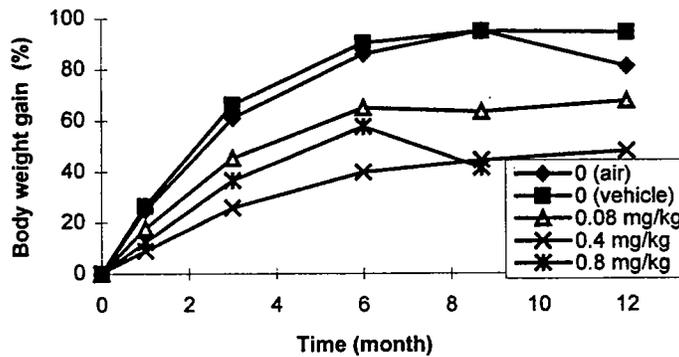


Figure 2b. Relative body weight gain (%) in the females. The corrected doses should be 0.04, 0.2 and 0.4 mg/kg/day for the low, mid and high dose groups, respectively.

Food consumption (weekly): Marginal decreases in food consumption was observed in the treated group.

Ophthalmology: Blepharitis were observed in the mid and high dose groups during second half of the treatment. According to the ophthalmologist, the blepharitis appeared to be an extension of the generalized skin lesions. The incidences of the blepharitis were as follows.

Time	Group	Incidences	
		Male	Female
Weeks 38	5	2/6	3/4
Week 43 & 52	4	0/2	4/4

EKG: No treatment-related effects were observed.

Clinical Pathology (Prior to treatment, weeks 13, 26, 37, 52):

Hematology: Slight to moderate decreases in lymphocytes numbers and increases in platelet numbers and white blood cells were observed (Table 22).

Table 22. Hematology in the 52 week inhalation toxicity study of triamcinolone in juvenile dogs

Groups	Male					Female				
	1	2	3	4	5	1	2	3	4	5
Dose(mg/kg/day)	0	0	0.04	0.2	0.4	0	0	0.04	0.2	0.4
Animals #	4	6	4	4	6	4	6	4	4	6
WBC (x 10 ³)										
week 13	10.3	10.4	9.4	10.7	9.7	9.7	11.4	10.1	9.2	11.5
week 26	10.4	10.9	9.5	11.4	12.1	10.6	13.5	11.1	9.6	13.3
week 37	12.4	-	-	-	14.2	11.2	-	-	-	16.3
week 52	10.4	10.9	9.3	12.9	-	15.0	13.7	10.5	11.7	-
Lymph (%)										
week 13	32.3	30.5	29.3	18.3*	21.2	29.8	30.0	29.3	18.8	18.7
week 26	32.8	31.5	30.8	16.3*	14.5*	34.0	31.0	27.8	18.3*	16.8*
week 37	15.0	-	-	-	10.3	28.5	-	-	-	10.5
week 52	26.5	21.5	27.8	11	-	19.5	26.3	30.5	22.5	-
Platelet (x 10 ³)										
week 13	287	346	305	383	302	308	355	368	375	413
week 26	278	331	289	387	361	320	346	360	382	428
week 37	377	-	-	-	394	330	-	-	-	440
week 52	262	327	280	434	-	393	400	397	464	-

* P < 0.05.

Clinical chemistry and urinalysis: No toxicologically remarkable findings were observed. Changes in several parameters were either minimal and were expected from chronic exposure of glucocorticosteroid. These changes included minimal decreases in serum ATS, minimal increases in serum alkaline phosphatase; and decreases in creatinine, osmolarity, sodium, potassium and chloride levels in the urine in the mid or high dose groups.

Organ weights: Table 23 summarizes group mean absolute organ weights. The absolute weights of adrenals, thymus, gonads, brain, lung and the spleen were decreased in the treated groups while absolute weight of liver was increased. The decrease in organ weights were accompanied by a decrease in body weight (in both the pre-terminally and the terminally sacrificed animals), although only the decreases in adrenal weights was statistically significant. Sample size may undermine the statistical significance of the findings. Chronic administration of steroids has been known to cause atrophy and decreases in organ weights of the adrenals, thymus and spleen.

Table 23. Organ weights in the 52 week inhalation toxicity study of triamcinolone in juvenile dogs

Groups	Male					Female				
	1	2	3	4	5	1	2	3	4	5
Dose(mg/kg/day)	0	0	0.04	0.2	0.4	0	0	0.04	0.2	0.4
Animals #	4	4	4	2	4	4	4	4	4	4
Terminal sacrifice										
Body weight (kg)	11.6	10.8	9.6	10.6		7.3	8.4	6.9	5.8	
Adrenals (g)	1.04	0.95	0.51	0.33		1.00	0.99	0.64*	0.38**	
Brain (g)	86.5	81.7	86.6	80.4		74.8	79.6	76.2	73.4	
Kidney (g)	61.8	55.1	49.8	61.0		43.3	40.2	35.4	36.3	
Liver (g)	325	312	290	386		277	254	220	241	
Lung (g)	114	99.2	89.9*	91.2		77.5	75.1	66.2	55.0*	
Gonads (g)	15.0	15.3	10.8	10.9		74.8	79.6	76.9	73.4	
Spleen (g)	84.0	70.3	72.7	55.3		47.3	65.5	44.0	35.6	
Thymus	5.69	5.31	2.64	1.69		4.49	3.48	2.74	1.53	
Interim sacrifice(n)										
Body weight (kg)		2			4		2			4
Adrenals (g)		10.1			9.4		8.0			6.1
Brain (g)		1.14			0.36		-			-
Kidney (g)		83.6			77.2*		76.3			68.9
Liver (g)		48.7			58.3		-			-
Lung (g)		332			451		263			287
Gonads (g)		98.3			77.9		77.2			50.1
Prostate		13.7			8.86		-			-
Spleen (g)		9.36			6.19		-			-
Thymus (g)		39.2			52.5		42.5			40.1
		1.38			0.78		5.87			1.12

* P < 0.05, ** P < 0.01.

Lung weight: Table 24 presents group mean weights of the lung and brain. Dose-dependent decreases in lung weight were also evident, although only the changes in the mid dose females and the low and high dose males were statistically significant. The absolute brain weight was significantly lower in the high dose males. The high dose animals seemed to have small lungs; both the absolute and relative lung weights (to brain weight and body weight) were lower than the controls.

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Table 24. Lung, brain and body weights in the 52 week inhalation toxicity study of triamcinolone in juvenile dogs

Groups	Male					Female				
	1	2	3	4	5	1	2	3	4	5
Dose(mg/kg/day)	0	0	0.04	0.2	0.4	0	0	0.04	0.2	0.4
Animals #	4	4	4	2	4	4	4	4	4	4
Terminal sacrifice										
Body weight (kg)	11.6	10.8	9.6	10.6		7.3	8.4	6.9	5.8	
Brain										
Absolute (g)	86.5	81.7	86.6	80.4		74.8	79.6	76.2	73.4	
Relative to body (g/kg)	7.56	7.67	9.05	7.65		10.5	9.48	11.43	12.76	
Lung										
Absolute (g)	114	99	90	91		77.5	75.1	66.2	55.0*	
Relative to body (g/kg)	9.94	9.16*	9.39	8.64		10.6	8.9	9.6	9.5	
Relative to brain (g/g)	1.32	1.22	1.04	1.15		1.03	0.94	0.86	0.75*	
Interim sacrifice(n)		2			4		2			4
Body weight (kg)		10.1			9.4		8.0			6.1
Brain										
Absolute (g)		83.6			77.2*		76.3			68.9
Relative to body (g/kg)										
Lung										
Absolute (g)										
Relative to body (g/kg)		9.69			7.82		9.56			8.37
Relative to brain (g/g)		1.18			0.93*		1.00			0.73

* P < 0.05.

Pathology:

Necropsy: Smaller thymus and testes, and skin lesions are seen in the mid and high dose groups (Table 25).

Table 25. Gross findings in the 52 week inhalation toxicity study of triamcinolone in juvenile dogs

Groups	Male					Female				
	1	2	3	4	5*	1	2	3	4	5*
Dose(mg/kg/day)	0	0	0.04	0.2	0.4	0	0	0.04	0.2	0.4
Animals #	4	4	4	2	6	4	4	4	4	4
Adrenal, small			1	2	6			1	3	4
Duodenum, area dark			1		1				1	2
Epididymis, small					3	-	-	-	-	-
Gall bladder, area raised				1	3					2
Kidney, enlarged					2	1				0
Lymph node discolorat'n			1	1	2		1	1	2	1
Skin lesions, various					4-6				3-4	3-4
Testis, small					3					-
Thymus, small/not found				1	6	1	1	1	3	4

* Preterminal sacrifice.

Histopathology: Microscopic findings are summarized in Table 26. Changes associated with triamcinolone treatment were the atrophy of the adrenal, thymus, lymph nodes and spleen in all dose levels of the treated groups. These changes corresponded to the gross observations of smaller organs. An increase in fat mass in the bones also occurred at all dose levels. In addition to the mentioned changes, skin inflammation, the thinning of the bones, skins and vagina occurred at mid and high dose groups. All the preterminally sacrificed animals (including the one

mid dose animal died of anesthesia) showed typical glucocorticosteroid effect: atrophy of the lymphoid organs and adrenal cortex, and changes in the skin, bone and bone marrow, and the reproductive systems.

Table 26. Incidences of microscopic findings in a 52 week inhalation toxicity study of triamcinolone in juvenile dogs

Groups	Male					Female				
	1	2	3	4	5*	1	2	3	4	5*
Dose(mg/kg/day)	0	0	0.04	0.2	0.4	0	0	0.04	0.2	0.4
Adrenal atrophy, cortical	0/4	0/6	3/4	4/4	6/6	0/4	0/6	2/4	4/4	6/6
Bone, trabecular thinn.	0/4	0/6	0/4	4/4	6/6	0/4	0/6	0/4	0/4	3/6
Bone, ↑ fat mass	0/4	0/6	3/4	4/4	4/6	0/4	0/6	2/4	1/4	3/6
Epididymis, ↓ sperm	0/4	1/6	0/4	1/4	3/6	-	-	-	-	-
Lymphoid atrophy, ile.	0/4	1/6	2/4	4/4	6/6	1/4	0/6	1/4	4/4	6/6
Liver, ↑ glycogen	0/4	0/6	0/3	3/4	4/6	0/4	2/6	0/4	1/4	4/6
Lung inflammation	3/4	6/6	3/4	3/4	6/6	3/4	2/6	2/4	1/4	1/4
Mammary gland atrophy	0/4	0/6	0/4	0/4	0/6	0/4	0/6	1/4	3/4	5/6
Nasal cavity lymph atro.	0/4	0/6	1/4	3/4	3/6	0/4	0/6	0/4	2/4	4/6
Ovary, corpora lutea abs	-	-	-	-	-	0/4	0/6	1/4	3/4	6/6
Skin inflammation	0/4	0/6	0/4	2/4	4/6	0/4	0/6	0/4	4/4	5/6
Skin atrophy	0/4	0/6	0/4	3/4	5/6	0/4	0/6	0/4	2/4	5/6
Spleen, lymphoid atrop.	0/4	0/6	0/4	3/4	1/6	0/4	0/6	1/4	2/4	4/6
Testis/vagina atrophy	0/4	0/6	0/4	1/4	3/6	0/4	0/6	0/4	2/4	6/6
Thymus atrophy, total	1/4	4/6	1/4	3/4	5/5	0/4	0/6	1/4	3/4	5/5
severe	0/4	0/4	0/4	1/2	5/5	0/2	1/6	0/4	2/4	3/3

* Pre-terminal sacrifice.

Lung histology: No treatment-related changes were observed. Bronchioalveolar inflammation (subacute and chronic) were prevalent in all animals including the controls (Table 26). Other incidental observations included pleura fibrosis, foreign body, granuloma/granulomatous inflammation, pneumonia.

Tracheal measurements: Table 27 presents tracheal measurements of the ring 10 in male and female dogs. Other ring measurement (rings 2, 20, and 30) were similar to the ring 10. Cartilage ring length decreased in a dose-dependent fashion, although ring measurements were not conducted in the high dose group.

Table 27. Mean tracheal measurements (ring 10) in the 52 week inhalation toxicity study of triamcinolone in juvenile dogs (mm)

Groups	Male					Female				
	1	2	3	4	5*	1	2	3	4	5*
Dose(mg/kg/day)	0	0	0.04	0.2	0.4	0	0	0.04	0.2	0.4
N	4	4	4	2	4	4	4	4	4	4
Lateral internal diameter	20.4	19.5	19.5	19.9	-	16.9	16.7	16.5	17.0	-
Dorsal internal diameter	16.2	15.6	16.4	15.5	-	13.6	13.9	13.3	13.3	-
Thickness of wall	2.1	2.6	2.0	2.0	-	2.0	1.9	1.8	1.7	-
Height of cartilage ring	4.5	4.1	3.9	3.9	-	3.7	3.5	3.3	3.6	-
Cartilage ring length	50.5	49.5	48.8	46.5	-	43.0	45.3	41.5	38.5	-

* Not measured due to preterminal sacrifice.

Plasma drug levels (day 1, and weeks 4, 38 and 52): Plasma triamcinolone levels of pre-

treatment and 1 hour post-treatment were determined by immunoradioassay (RIA) by [redacted]. The quantifiable range was 0.025 ng/ml to 3.20 ng/ml. Samples with triamcinolone concentrations greater than the upper quantification limit was diluted and reassayed. Table 28 present the results on day 1. There appeared no difference in Cmax in gender and duration of dosing.

Table 28. Mean Plasma triamcinolone levels (nmol/L) 1 hour post-dosing in a 52 inhalation study in juvenile dogs

<u>Dose *</u>	<u>0.04 mg/kgday</u>	<u>0.2 mg/kgday</u>	<u>0.4 mg/kgday</u>
Male	0.51	3.39	24.9
Female	0.70	3.52	37.0

* Inhaled doses. # Range.

Note: Approximately 14% of the animals in the control groups contained plasma triamcinolone concentration of greater than 0.1 nmol/ml periodically. The [redacted] report indicated that the reason for the detection of triamcinolone in the control animals were unknown.

Comment: Hernia was observed in the mid and high dose animals (1/8-MD, 3/12-HD). The sponsor claimed that this observation is not treatment-related. However hernia in juvenile dogs was also present with another steroid - fluticasone (NDA [redacted]). The only difference was that the fluticasone study had a higher incidence (13/24-treated verses 0/24-control). These observations suggest that hernia could be a toxicological effect associated with steroid treatment in juvenile dogs. Hernia was not present in the adult dogs in both the fluticasone and budesonide studies (NDA [redacted] & 20441).

Summary: Juvenile beagle dogs exposed by oral inhalation to [redacted] formulation at 0.04, 0.2, and 0.4 mg/kg of triamcinolone for 1 year showed typical effects of glucocorticosteroids: immunosuppression and growth suppression. These were indicated by 1) the atrophy of the thymus, adrenal cortex and lymph nodes, 2) increases in the incidences of skin infection, 3) inhibition of the development of the reproductive system, and 4) the reduction of body size and body weights. The reduction in body size was associated with decreases in the weights of several major organs. Clinical pathology changes included minimal to mild increases in white blood cell count, decreases in the percentage of lymphocytes, increases in platelet numbers and other changes usually associated with glucocorticosteroids. Clinical signs included deterioration of general conditions, skin infections, hernia, and mortality. No NOAEL value was established.

Summary of Inhalation Toxicology of Triamcinolone HFA-134a MDI

Toxicity of Triamcinolone HFA-134a MDI formulation was evaluated by inhalation/intranasal routes of exposure for a duration of up to one year in rats and dogs. Triamcinolone dose levels were 5 to 80 $\mu\text{g}/\text{kg}/\text{day}$ in rats and 22 to 400 $\mu\text{g}/\text{kg}/\text{day}$ in dogs, respectively. These studies revealed a dose-dependent toxicity profile of triamcinolone. At low doses major toxicological findings were growth retardation and immunosuppression, while a variety of organs and systems may be affected at higher doses. The overall toxicological findings, however, were similar to previous studies with other triamcinolone formulations and were also typical of a steroid.

In a 4-week oral inhalation study, beagle dogs (4/sex) were dosed with triamcinolone at 40, 200, and 400 $\mu\text{g}/\text{kg}/\text{day}$ (pulmonary deposition). Treatment-related effects are concentrated in the mid and high dose groups: thymus and adrenal atrophy accompanied by decreases in the organ weights, decreases in food consumption and a slight weight loss (HD only). Other changes included a dose-related, but statistically non-significant increase in liver weight, and decreases in lung and spleen weights. The low dose animals showed thymus atrophy and decreases in thymus weight only. All parameters returned to normal after a recovery period of 2 weeks (2/sex in high dose and vehicle control only). No NOAEL value was established.

In a 3-month nose-only inhalation study, Sprague-Dawley rats were exposed to the drug at 5, 20 and 80 $\mu\text{g}/\text{kg}/\text{day}$ (total body exposure), corresponding to the expected pulmonary exposures of 1.2, 4.3, and 18 $\mu\text{g}/\text{kg}/\text{day}$ for the low, mid, and high doses, respectively. A classic manifestation of steroid effects were observed. A dose-related and statistically significant decreases in body weight during the study was found in all treated groups, compared to the controls. The high dose females actually lost weight compared to the beginning of treatment. Clinical pathology changes included decreases in white blood cell counts, lymphocytes, urine osmolarity, potassium, and creatinine; and increases in neutrophils, serum AST, ALP, total bilirubin, phosphorus. Weights of many major organs were decreased with dose while the liver weight was increased. Microscopic changes included dose-related increases in the incidencies of atrophy of the adrenal, thymus, spleen, lymph node, and skin. Increases in the incidences of stromal fat in the bone marrow, pigmentation of kupper cells in the liver and vaginal mucification were seen in the mid and high dose groups. Thinning of the bone was seen in the high dose group only. Again, No NOAEL was established.

In a 3-month intranasal toxicity study, beagle dogs (3 - 4/sex) were given 22, 44 and 88 $\mu\text{g}/\text{kg}/\text{day}$ of the drug by instillation. Histological examinations were conducted in the upper respiratory tract only. Similar to the 4 week study, a slight decrease in body weight was seen in high dose females. Decreases in adrenal and thymus weights (microscopic changes in the thymus and adrenals were unknown) were seen in the mid and high dose groups. Also observed was atrophy of lymphoid tissues in both the nasal cavity and nasopharygeal regions. All parameters, with the exception of the adrenal weight, returned to normal after a recovery period of 4 weeks. The NOAEL value for the nasal cavity was 22 $\mu\text{g}/\text{kg}/\text{day}$.

In a 1-year oral inhalation study, juvenile beagle dogs (4 - 6/sex/dose) were exposed by oral inhalation at pulmonary deposition of 40, 200, and 400 µg/kg for the low, mid and high dose groups, respectively. Mortality and preterminal sacrifices occurred as early as 6 months of treatment in the mid and high dose groups. By 9 months of treatment, all the high dose animals had to be sacrificed due to their poor general condition and demodecosis (a parasitic disease). Again, the atrophy of the thymus and lymph nodes, and increases in the incidences of skin infection, hernia, the reduction of body size and body weights, decreases in the weights of several major organs were observed. Clinical pathology included minimal to mild increases in white blood cell count, decreases in the percentage of lymphocytes, increases in platelet numbers. Although most observations occurred in the mid and high dose groups, steroid effects were also evident in the low dose group. These included adrenal atrophy, lymphoid tissue atrophy, and increased stromal fat of the bone marrow. Once more, no NOAEL value was established.

In conclusion, the toxicological profile of triamcinolone HFA-134a formulations is similar to previous observations (See previous review section).

Note:

This one-year toxicity study of triamcinolone in juvenile dogs was conducted under the request by the Agency upon the observation that chronic beclomethasone treatment induced misshaped trachea in dogs (NDAs 125-121 and 20-121). The triamcinolone study, however, failed to confirm such an observation. Nonetheless, at the port of entry, the lungs are of especial interest. Inhaled steroids have recently been promoted to replace bronchodilators as the first line of treatment for asthma (*Guidelines for Diagnosis and Management of Asthma, 1997, Expert Panel 2, NIH Publication No. 97-4051, National Institute of Health*). This is partially due to the potential cardiovascular effect associated with bronchodilators and partially because of the systemic toxicity of the inhaled steroids. Clinical literature evaluation of adverse effects of inhaled steroid, however, are more concentrated on HPA-axis suppression and growth retardation (Kamada et al, *Pulmonary Pers.*, 1996;153:1739-1748) and thus, the effect on the lung growth and development is less known. Preclinical evaluation of the lung is mostly limited to the heavy emphasis of histological changes. Effect on growth and development of then lung is also unknown. A thorough evaluation of lung growth and/or development would be helpful to identify potential safety concerns. The lack of data in the literature warrants such an effort.

The exploration of possible effects of triamcinolone on the lung was accomplished by examining 1) lung size, 2) tracheal measurement, and 3) microscopic changes. The lung size was evaluated by its weight which may be a very imprecise measurement of the lung growth. Table 29 summarizes absolute and relative lung weights as a function of triamcinolone dose in the repeated-dose studies in dogs. Noticeably, all studies showed that the triamcinolone-treated animals had a reduction in both relative and absolute lung weights when compared to the air control. These reductions were generally dose-related although the statistical significance was

rarely achieved (the high dose females in the one year toxicity study). It should also be pointed out that sample sizes of these studies are rather small ($n = 3 - 4/\text{sex}/\text{dose}$).

Table 29. Summary of the changes in lung weights compared to the control in dogs (%)

Study No.	Weight	duration	Route	$\mu\text{g}/\text{kg}/\text{day}$	Treatment				
					Control	Vehicle	Low dose	Mid dose	High dose
94-119	Absolute	4 wk	IH*	40, 200, 400	-	↓ 9.9	↓ 4.2	↓ 16.4	↓ 14.3
	Relative@				-	↓ 4.8	-	↓ 13.0	↓ 10.9
93-004	Absolute	13 wk	IN	20, 44, 88	-		↓ 18.5	↓ 17.2	↓ 18.3
	Relative				-		↓ 10.9	↓ 7.5	↓ 11.9
92-055	Absolute	52 wk	IH	40,200,400	-	↓ 8.1	↓ 17.8	↓ 24.6	↓ 27.9
	Relative				-	↓ 8.8	↓ 7.1	↓ 11.7	↓ 14.9

* IH = inhalation administration, IN = intranasal administration.

@ Relative to body weight.

Steroids are known to cause growth retardation. The decrease in the absolute lung weight is an expected event because steroids-treated animals are found to be smaller. It, however, assumes that 1) the steroids lack direct effects on the lung; 2) growth retardation is a sequela of the systemic exposure rather than the local exposure, 3) the lung weight is proportional to body size. If these assumptions hold, one would find that the steroid treatment cause a reduction in the absolute lung weight, but not in the relative lung weight. Surprisingly, relative group mean lung weight was also decreased with the triamcinolone treatment. The reduction in relative lung weight suggests that inhaled triamcinolone may also have a direct effect on the lung growth. Further evaluation of this observation was conducted by comparing individual data. Figure 3 presents the individual absolute lung weight and the corresponding body weight of the one-year inhalation study in juvenile dogs. It also shows that the treated animals seemed to possess smaller lungs when compared to the control animals of the same body weight. A comparison of relative lung weight to brain weight dose not yield additional information than the comparison of absolute lung weight.

The effect of triamcinolone treatment on lung growth was further evaluated by examining the tracheal measurements. Table 27 presents tracheal measurements in the one-year study in dogs. Despite the lack of data in the high dose group, dose-dependent decreases in tracheal diameter and wall thickness, and decreases in the tracheal ring lengths and heights were apparent in the mid and low dose groups. These changes correlate well with the body size and the lung weight, but histological changes of the lung were absent. The lack of histological change in the lungs is probably not surprising as the lung development in these animals is expected to be completed prior to commencement of the treatment. Altogether, the smaller body size, the smaller lung and the shorter low respiratory tract and the absence of histological changes suggest chronic inhalation of triamcinolone suppress lung growth.

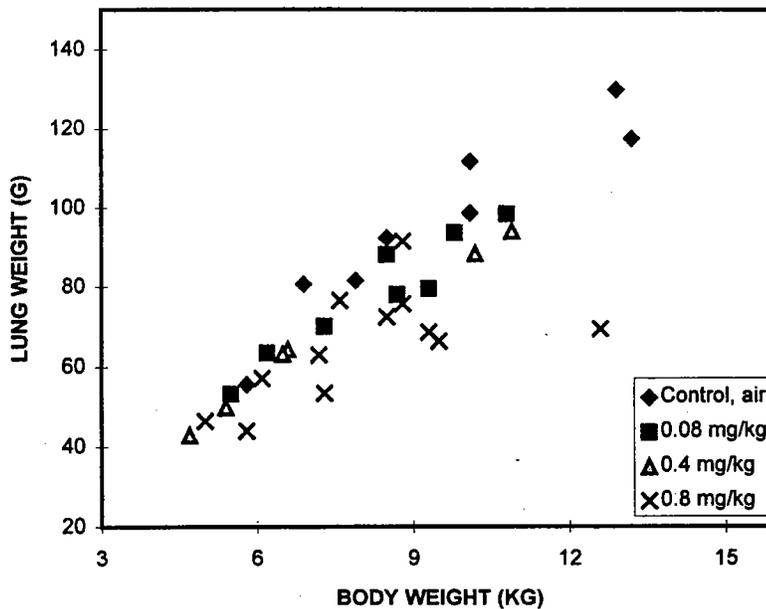


Figure 3. Lung weight as a function of the body weight in a 52-week inhalation toxicity study of triamcinolone. There appeared to be no sex difference in lung weight versus body weight between males and females.

An additional evaluation was conducted by comparing organ sensitivity and reversibility of the damage of tissue damage. Tissue sensitivity was evaluated by the severity of growth retardation in the low dose animals in the 1-year study because of the milder manifestation of triamcinolone toxicity. The decreases in mean relative organ weights were: adrenal (\downarrow 35 - 41 %), thymus (\downarrow 34 - 43%), gonads (\downarrow 15 - 18%), and the lung (6 - 9%). Histological changes were limited to the atrophy of the adrenal (5/8) and thymus (2/8). The lack of morphological changes in the lungs suggests that adrenals and thymus be the most sensitive tissues and that lung be less sensitive. However, atrophy of the cortex and thymus is usually reversible upon cessation of the drug in animals. On the other hand, the reversibility in lung growth is unknown.

Growth retardation by glucocorticosteroids in children is well known (*Goodman and Gilman's Pharmacological Basis of Therapeutics, 1996, p 1476; and Kamada et al., Pulmonary Perspective 1996, -153:1739-1748*). The observation that the treated-animals possess the smaller lungs does not seem to be unique to triamcinolone. Other steroids including beclomethasone and fluticasone showed similar findings (INDs _____ and NDA 20121). This observation was also consistent with an earlier report that postnatal administration of cortisone (IP) for 11 weeks suppressed development of lung and trachea in ferret (Ellington et al., *J. Appl. Physiol.*, 1990;68:2029-2033). Finally, Picken et al (1974) reported that methylprednisolone treatment increased elastic recoil in rat lung (*Am Rev Respir Dis*, 110:746755). Relevance of these findings to humans are unknown. The effect of inhaled steroids on lung growth and/or development may need further exploration.

One interesting observation in the triamcinolone toxicity studies is that the 2 dog studies (4 and 52 weeks) that employ a vehicle control group show that vehicle caused a slight (but statistically non-significant) decrease in both the mean absolute (8 - 10%) and relative (5 - 9%) lung weights. Histological changes are absent. Similar effects were apparent in other studies (IND — using a similar vehicle. The magnitude of this change may not be biologically significant to cause safety concern about this application. However, this change was not observed in the Drug Master File of the — Review of Dr. Misoon Chun on 9/28/94). Excipients in the to be marketed formulation consists of HFA-134a (—) and a small amount of alcohol (—)

OVERALL SUMMARY AND EVALUATION

The RPR also has other triamcinolone products currently on the market: Nasacort AQ Nasal Spray Nasacort (NDA 20-468), Nasacort® Nasal Inhaler (NDA 19-798), and Azmacort® Oral Inhaler (NDA 18-117). They were approved during the period of in 1982 to 1994.

The first triamcinolone drug product was approved in 1957. In addition to the RPR products, there are also other triamcinolone products on the market in various dosage forms: tablet, injections, syrup, eye-ear solution, nasal spray, and metered dose inhalers. Safety of triamcinolone has been established by previous preclinical investigations and extensive clinical experience.

The following is a summary of preclinical data of Nasacort and Azmacort Products. Detailed information can be found in the reviews by Dr. Virgil Whitehurst in NDA 20-468 (September 25, 1995) and Dr. Conrad Chen in NDA 18-117 (November 30, 1978) and early sections in this review.

Pharmacology: Triamcinolone is a glucocorticosteroid agonist that possesses antiinflammatory activity and a variety of other activities. Triamcinolone inhibits croton oil-induced ear inflammation (PO) and asbestos pellet-induced granuloma formation (SC) in rats. Clinical efficacy of the drug in respiratory diseases has been showed by clinical trials and experience.

Pharmacokinetics: Triamcinolone is rapidly absorbed after oral, intranasal and inhalation administration. Peak plasma levels are reached 0.8 - 2 hours post dosing in rats, dogs and monkeys. With intranasal administration, the highest drug concentrations are found in the nasal cavity, intestine and liver soon after dosing. At least one-third of the initial concentrations is found in the nasal cavity 4 hours post dosing. No drug can be detected in the nasal cavity, nor in

the plasma 24 hours post dosing. The drug is primarily metabolized in the liver. Major metabolites are 6 β -hydroxy-TAA and 21-carboxylic acid of 6 β -hydroxy-TAA across species. A major portion of the drug is eliminated through feces. Less than 5% of total dose is eliminated through the urine in dogs. Half-lives of the drug are 3 - 7 hours in rats and dogs after oral and IV administration. About 68% of the drug in plasma is protein bound in humans.

Toxicology:

General toxicity: Preclinical investigations with other formulations demonstrated that LD50 values were 28 mg/kg in rats (IP) and 132 mg/kg in mice (SC). Chronic administration of triamcinolone (SC, PO, IH, IN in rats, dogs, rabbits and monkeys) may result in hypothalamic-pituitary-adrenal (HPA) axis suppression, growth retardation, immunosuppression, enhanced bone resorption, alterations in carbon hydrate metabolism, hernia, behavior changes, and other effects known to be associated with steroids. HPA axis suppression is indicated by atrophy of adrenal cortex. The growth retardation is demonstrated by the decreases in body sizes and the sizes of major organs, including the inhibition of the development of the reproductive system. The immunosuppression is characterized by atrophy of the lymphoid tissues: the thymus, spleen, lymph nodes, and the increases in the incidences of skin infection. Enhanced bone resorption could result in osteoporosis. Hernia occurs at high doses in juvenile dogs.

Studies (5) submitted in this application demonstrate that toxicity profiles of the triamcinolone-HFA-134a formulations are similar to the previous CFC formulations. No unexpected toxic responses are identified. Toxic responses of the HFA-134a formulations also include HPA axis suppression, growth retardation, immunosuppression, and other glucocorticosteroid effects. The severity of toxicity of the HFA formulations may be comparable and/or slightly higher than the previous formulations. However, a head-to-head comparison of toxicities between formulations is not possible because of experimental design. Nonetheless, the available data indicate target organs of toxicity, tissue responses, and toxicity profiles of the HFA-134a formulation similar to the CFC formulation.

Special toxicities: Carcinogenicity, and effect on reproduction has been evaluated and reviewed.

Carcinogenicity: Triamcinolone is not carcinogenic in 2-year gavage studies in rats and mice. The respective dose levels were 0.05, 0.2 and 1.0 $\mu\text{g}/\text{kg}/\text{day}$ in rats and 0.1, 0.6 and 3.0 $\mu\text{g}/\text{kg}/\text{day}$ in mice. They correspond to approximately 0.2, 1.0 and 6 % of the recommended clinical dose on a $\mu\text{g}/\text{m}^2$ basis.

Mutagenicity: Mutagenesis studies with triamcinolone acetone have not been carried out.

Reproductive toxicity: Triamcinolone has been shown to be teratogenic in rats, rabbits and monkeys. Rats and rabbits at inhalation doses of 20, 40 and 80 $\mu\text{g}/\text{kg}$ showed cleft palate and/or internal hydrocephaly and axial skeletal defects. Rats at oral doses of 5.0 $\mu\text{g}/\text{kg}/\text{day}$ and above showed dystocia, prolonged delivery, increases in fetal resorptions and stillbirths, and decreases in pup body weight and survival. At an oral dose of 1.0 $\mu\text{g}/\text{kg}$, no teratogenic effects were

observed in rats. Monkeys at an inhalation dose of 500 µg/kg showed cranial malformations. No evidence of impaired fertility was manifested at oral doses of up to 15.0 µg/kg in rats.

Excipients:

Excipients in the to be marketed formulation consist of HFA-134a and a small amount of alcohol. Toxicity profiles of HFA-134a have been established previously (DMF Review of Dr. Misoon Chun on 9/28/94). A daily dose of less than 20 actuations/individual is considered safe in humans. The maximum daily dose per individual (8 actuations) is below the acceptable level. Ethanol in the new formulation was also well below the acceptable levels of . Therefore, the excipients individually do not pose significant safety concerns. However, safety of a combination of the 2 chemicals is less known. Two dog studies (4 and 52 weeks) showed that the excipient group animals had a slight, statistically non-significant decrease in both the mean absolute (8 - 10%) and relative (5 - 9%) lung weights, compared to the air control (See table 29). Histological changes, however, were absent. The small sample size and minor changes may not be biologically significant to cause safety concern about this application.

Impurities and extractables:

The sponsor has not submitted information on impurities and/or extractables in this drug product. Dr. Craig Bertha, the Chemist Reviewer, has requested the sponsor to submit this information. Safety evaluation of the impurities and extractables will be conducted upon reception of the requested information.

Conclusion:

Nasacort® FHA-134a uses triamcinolone as the active ingredient and the HFA-134a as the replacement of the CFC as the excipient. Triamcinolone has been on the market for over 40 years (11 NDAs) and extensive clinical experience is available. Safety of triamcinolone in CFC and other formulations has been established by previous clinical and non-clinical studies. Chronic administration of triamcinolone induces HPA-axis suppression, growth retardation, immunosuppression, and other effects known to be associated with chronic use of steroids. Reproductive studies in rats, rabbits and monkeys showed triamcinolone is teratogenic. Carcinogenic studies in rats and mice demonstrated no carcinogenic potential, although mutagenicity potential of triamcinolone acetate have not been evaluated. Most carcinogenic steroids are known to be non-genotoxic and act through promotion mechanisms. The lack of carcinogenic potential of triamcinolone in the 2-year rodent bioassays and the known tumorigenic mechanisms of hormonal drugs suggest that the drug is likely to be a non-genotoxic compound. Therefore, the lack of an characterization of mutagenic potential of the drug should not prevent approval of this application.

As discussed above, safety of the Nasacort® CFC formulations have been established. The sponsor conducted several inhalation and/or intranasal toxicity studies to bridge toxicity profiles of the HFA-134a formulations. These studies did not reveal any unexpected toxic responses of triamcinolone and suggested that toxicity profiles of the HFA-134a and CFC formulations may be similar. Safety of the excipients (HFA-134 and alcohol) have been established previously.

Toxicity studies in the submission meet divisional requirements during the pre-NDA in March 1, 1995. These laboratory animal studies show that the toxicological profiles of the new formulation - Nasacort® HFA-134a - are similar to that of previously approved CFC products. Clinical trials indicate that plasma triamcinolone AUCs of the new formulations are comparable to the CFC formulations in humans. The existing data are sufficient to support safety of the proposed HFA-134a MDI — However, safety of impurities and extractables in this product has not evaluated fully.

Labeling review:





Recommendation:

This Nasacort® HFA-134a MDI application is approvable from the preclinical viewpoint. However, final approval may be recommended upon a thorough evaluation of the safety of the impurities and extractable in the product when the information is submitted.

Luqi Pei 10/2/97

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Hilary Sheevers
10/4/97

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Revised by Dr. Hilary Sheevers on 8/22/1997, and 9/10/97.

cc: HFD-570/Division File
HFD-570/ Pei/ Anthracite/ Sheevers/ Himmel
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