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RESEARCH**

APPLICATION NUMBER:

20-784

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-784	Date of Submission: December 16, 1996 (Original submission) November 30, 2001 March 21, 2003 October 6, 2003 (current) January 14, 2004 (label) February 11, 2004 (label)
<u>Generic Name</u>	Triamcinolone Acetonide
<u>Brand Name:</u>	Nasacort® HFA
<u>Formulations:</u>	Aerosol
Route of Administration:	Nasal
Indication:	Seasonal and Perennial Allergic Rhinitis
<u>Type of Submission:</u>	NDA/New formulation (HFA Propellants)
<u>Sponsor:</u>	Aventis Pharmaceuticals
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.
Date of Submission:	December 16, 1996 (original date of submission)
Date Received:	January 12, 2004
Review Date:	January 29, 2004
First Draft	February 2, 2004
Second Draft	February 4, 2004
DFS Draft:	February 26, 2004

Background:

This NDA is for a new formulation using HFA-134a propellants in place of chlorofluorocarbon (CFC) that is used in the currently marked product (Nasacort AQ).

What is the History of this NDA?

Nasacort (triamcinolone acetonide, TAA) was originally approved as nasal inhaler in July 11, 1991 (NDA 19-798). The original product contains chlorofluorocarbon (CFC) as propellant. Nasacort AQ is indicated in the treatment of seasonal and perennial allergic rhinitis symptoms in adults and children 6 years of age and older.

The new formulation for Nasacort HFA (triamcinolone acetonide nasal aerosol) was originally submitted by Rhone-Poulenc Rorer (RPR) on December 16, 1996. Nasocort HFA is the first nasal MDI propelled by HFA propellants submitted to the Agency. Its development was spurred by the Montreal Protocol on Substances that Depleted the Ozone Layer which mandates a worldwide phase-out of the use of CFCs. This NDA was subjected to four main review cycles as summarized in **Table 1**.

Table 1. Summary of Nasacort HFA Main Review Cycles

Date of Submission	Action Letter	Date of Response to To Action	Action	Deficiencies
12/16/1996	12/16/1997	11/30/2001	Approvable	CMC
11/30/2001	5/31/02	3/21/2003	Approvable	CMC
3/21/2003	9/23/03	10/6/2003	Approvable	CMC
10/6/2003	pending	-	-	-

It should be noted that many issues and delays were encountered due to the change in the ownership of this NDA from RPR pharmaceuticals to Aventis Pharmaceuticals. Therefore, the sponsor's responses to original action letter, subsequent action letters, and several information request letters were delayed by several years. The main deficiencies outlined in each action letter were related to CMC (see chemistry reviews).

Is There Any Pre-clinical Issues?

The sponsor conducted pre-clinical toxicology studies to bridge the data between the CFC based and HFA based Nasacort products. Overall these studies did not show any new toxicological concern. Therefore, from the pre-clinical perspective, the NDA was approvable with some labeling changes (see Dr. Pei original review).

What is the Current Status of the CMC Issues?

From the CMC perspective, the application was not approved. There were numerous deficiencies with regard to CMC. These deficiencies were conveyed to the sponsor in the all action letters, several subsequent communications, and re-submissions. In the most recent review dated January 16, 2004, the recommendation was approvable. At this time, all CMC deficiencies have been addressed by the sponsor throughout the four reviews cycles. Nevertheless, additional Phase IV commitments have been agreed on with the sponsor (see Dr. Graig Bertha chemistry review).

What is the Proposed Rate of Delivery/Dose?

From the CMC perspective, the aerosol should be delivering 55 mcg per actuation to each nostril. Two actuations (110 mcg) to each nostril are recommended per day as an initial dose level (i.e., a total dose of 220 mcg per day). The maximum daily dose is 440 mcg once daily.

What Clinical Studies Have Been Conducted For Nasacort HFA?

As indicated above, the proposed indication for Nasacort HFA is for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis. This is the same indication that is currently approved for the CFC-based MDI formulation of Nasacort AQ. In the original NDA, the sponsor submitted the following clinical studies:

- Single dose crossover PK/BE study to compare the Nasacort HFA to Nasacort CFC
- Two-week, double-blind, placebo-controlled comparison of Nasacort HFA and Nasacort CFC in patients with seasonal allergic rhinitis.
- One-year open label study to demonstrate the long-term safety of Nasacort HFA.

The clinical studies show comparability between the two formulations: the currently marketed CFC product and the new HFA product. In his memorandum dated December 17, 1997, Dr. John Jenkins, the former Director, Division of pulmonary Drug Products, stated that there are no outstanding clinical issues and the NDA is approvable from the clinical perspective with appropriate labeling changes (see also original clinical reviews by Dr. Honig and Kwong).

What Clinical Pharmacology Study Have Been Submitted?

Summary:

As stated in the above section, one PK/BE study was submitted in the original NDA (study # RG5029T-123). Additional PK data were crossed reference to the original NDA (#19-798). The objective of this study was to demonstrate the systemic bioequivalence/exposure of triamcinolone from the new HFA and old CFC based products (see original review dated July 3, 1997 by Dr. Chen).

From this study the systemic exposure to triamcinolone following 440 mcg dose of Nasacort HFA was comparable to that following 440 mcg from Nasacort CFC.

What is the Formulations Composition?

The following table shows the composition of each formulation used in the original PK/BE study:

Table 2. Formulations Composition Used the Original PK/BE Study (#RG5029T-123)

Formulation	A (HFA-134a)		B (CFC-P12)	
	Quantity	%, W/W	Quantity	%, W/W
Triamcinolone Acetonide, USP Micronized Topical Grade	15.0 mg	—	15.0 mg	—
Dehydrated Alcohol, USP	—	—	—	—
CFC (P-12)	—	—	—	—
Tetrafluoroethane (HFA 134-a) Pharmaceutical Grade	—	—	—	—

What was the Study Design?

The dose used in this study was 440 mcg of triamcinolone acetonide (TAA) which corresponds to 4 actuations per each nostril (i.e., each actuation delivers 55 mcg of TAA). A total of 24 healthy male subjects participated in this study. This was a crossover design study. Each subject received one of each formulation (HFA or CFC) with a washout period of one week. The final-to-be marketed Nasacort HFA formulation was used in this study. Blood samples were collected at appropriate time intervals over 24 hours.

What Were the Results?

Figure 1 and Table 3 show the summary of the PK/BE data from the original study. From this data, triamcinolone exposure from both formulations was comparable.

Figure 1. Mean plasma concentration-time profiles Following Nasacort HFA or Nasacort CFC in Healthy subjects (figure copied as is from the original NDA submitted by the sponsor in 1996).

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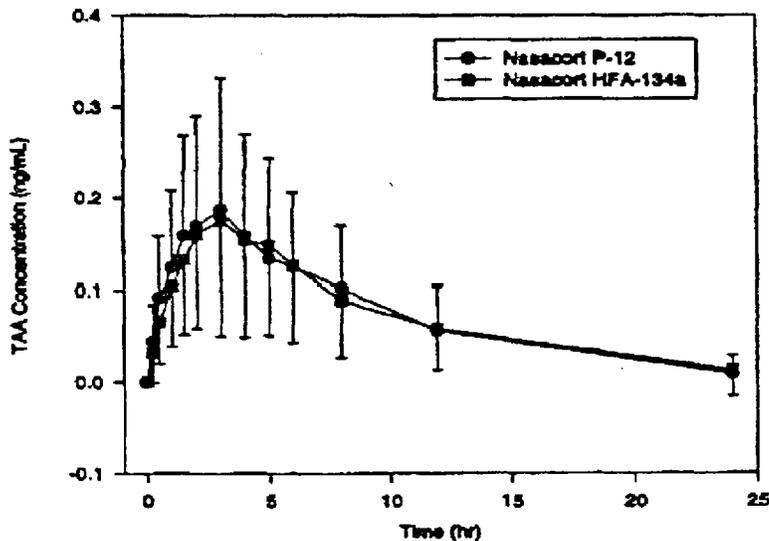


Table 3. Mean PK and BE Parameters Following Nasacort HFA or Nasacort CFC in Healthy subjects (table copied as is from the original NDA submitted by the sponsor in 1996). Formulation A=HFA and Formulation B =CFC

Parameters (n=23) ^a	Formulation A	Formulation B	Ratio ^b	90% Cis	Pass/Fail
C _{max} (ng/ml)	0.196 (58.1) ^c	0.205 (68.2)	96.7	82.1-111.3	Pass
T _{max} (hr)	3.8 ^d (63.8)	2.7 (47.7)	-----	-----	-----
AUC ₀₋₁₂ (ng-hr/ml)	1.31 (63.1)	1.36 (70.2)	97.6	83.5-111.7	Pass
T _{1/2} ^e (hr)	4.1	5.2	-----	-----	-----

- a. Subject # 13 was considered as a statistical outlier and excluded from analysis.
- b. The Ratio of A/B x 100%.
- c. Coefficient of Variation (CV%) calculated as SD/Mean x 100%.
- d. Significantly different from 2.7 hr (P<0.05).
- e. Apparent terminal half-life (harmonic mean).

Based on the 90% CI data for the C_{max} and the AUC_{0-12h}, the sponsor believes that the two formulations are considered bioequivalent (Table 3). However, the data was based on AUC_{0-12h} rather than AUC_{0-∞} as generally required and preferred parameter to establish bioequivalency. Therefore, based on the regulatory standard and BE acceptance criteria, the two formulation are considered not bioequivalent. The original OCPB review also concluded that the two formulations are not bioequivalent, since it was based on AUC_{0-12h} rather than AUC_{0-∞}. There was a high variability in the data as shown by the high %CV in the Table 3 (>50%).

What Were the Main OCPB Comments From the Original Review?

1. The two formulations are not bioequivalent based on the Agency's current bioequivalency acceptance criteria.
2. The reviewing medical officer should, therefore, make a final decision on the approvability of the new formulation.
3. The Cmax and AUC (exposure) from the HFA formulation is lower than that of the CFC formulation.
4. The Tmax value for the HFA formulation is 3.8 h (with larger %CV) which is significantly different from the CFC formulation, 2.7 h (with smaller %CV).
5. The AUC_{0-∞} should have been used in the statistical analysis instead of AUC_{0-12h}.
6. One subject was considered an outlier by the sponsor. This was acceptable to OCPB.
7. Other minor comments were related to handling and retention of blood samples.
8. In terms of labeling comments, _____

No specific PK labeling comments were made by the reviewer at that time.

Are There Any OCPB Outstanding Issues From the Original NDA?

It is noted that most of the above comments were conveyed and discussed with the sponsor during the original review cycle and subsequent communication. Therefore, at the time of completion of the review, it does not appear that there are any outstanding issues from OCPB perspective.

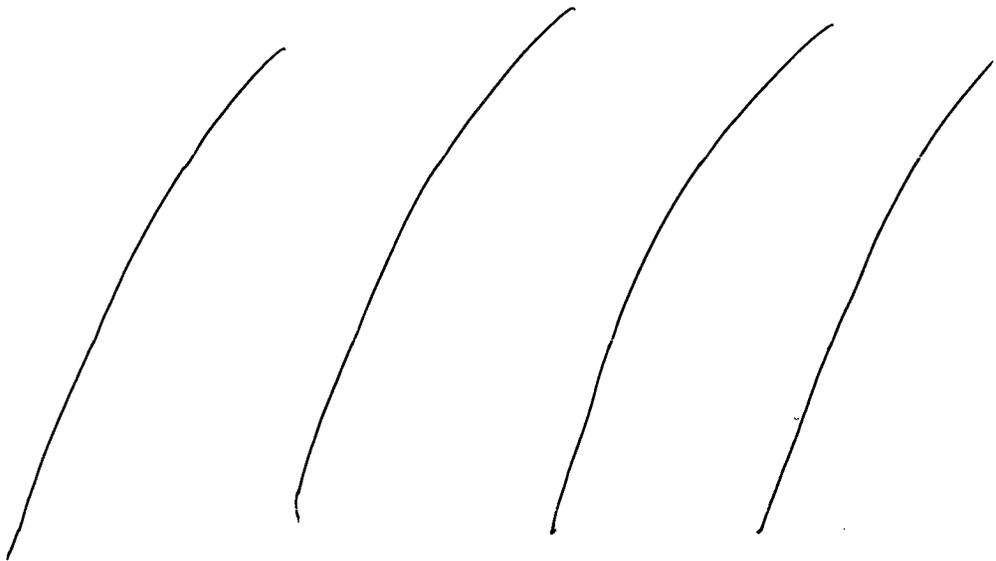
What Are the Current Labeling Comments?

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 Draft Labeling

 Deliberative Process



RECOMMENDATION:

From OCPB perspective, the information submitted in the original NDA and subsequently is acceptable. Please convey the above labeling comments to the sponsor.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader-----

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

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

/s/

Sayed Al-Habet
3/3/04 09:01:37 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
3/3/04 09:59:53 AM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 20-784
Triamcinolone Acetonide

SUBMISSION DATE:
12/17/96 (Serial No. N000)

BRAND NAME:
Nasacort Nasal ← (55 µg/actuation)

SPONSOR: Rhône-Poulenc Rorer

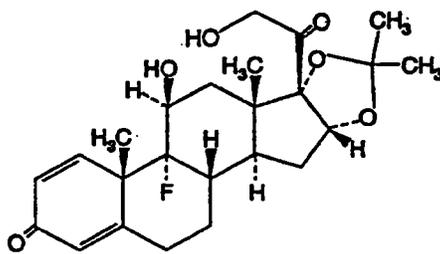
REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Switch of an Approved CFC Formulation to a New HFA Formulation Code:3S

TITLE: "Review of a Pharmacokinetic Bioequivalence Study for a New HFA Formulation and a Currently Marketed CFC Formulation of Nasacort Nasal — (Study No. No. RG5029T-123)"

SUMMARY:

NDA 19-798 for Nasacort (triamcinolone acetonide, TAA) Nasal Inhaler that used P-12, a chlorofluorocarbon (CFC) propellant, was approved on 07/11/91. TAA is a synthetic glucocorticoid with anti-inflammatory and anti-allergin properties. Its chemical structure is shown below:



Because the CFC propellant may be contributing to the depletion of the stratospheric ozone, the sponsor, Rhône-Poulenc Rorer (RPR), therefore, reformulated the currently marketed Nasacort Nasal Inhaler using a non-CFC propellant, HFA-134a. To comply with the regulation for switching from CFC formulation to HFA-134a formulation of Nasacort Nasal Inhaler, RPR conducted a bioequivalence (BE) study. NDA 20-784 for Nasacort HFA Nasal Inhaler was submitted for review on 12/17/96 by RPR. The same indications for seasonal and perennial allergic rhinitis symptoms in adults and children 6 years of age and older are currently being sought. Please see the package insert (PI) in Appendix 2 for details.

Under Human Pharmacokinetics/ Bioavailability (PK/Bio) section, submitted was the above BE study (No. RG5029T-123) plus PK information which is cross-referenced to NDA 19-798. In Study No. RG5029T-123, a single dose of 440 µg TAA (4 actuations per each nostril) was given to 24 healthy male volunteers in a crossover fashion with a washout period of one week. Their mean (± standard deviation, SD) age, body weight (BW), and height were 25.9 (± 8.2) years old, 169 (± 20) lb, and 71.2 (± 2.2) in, respectively.

The to-be-marketed HFA formulation (Formulation A) was compared with the currently marketed CFC formulation (Formulation B; Table 1) for systemic TAA exposure.

Table 1:

Formulation	A (HFA-134a)		B (CFC-P12)	
	Quantity	%, W/W	Quantity	%, W/W
Triamcinolone Acetonide, USP Micronized Topical Grade	15.0 mg	—	15.0 mg	—
Dehydrated Alcohol, USP	—	—	—	—
CFC (P-12)	—	—	-----	-----
Tetrafluoroethane (HFA 134-a) Pharmaceutical Grade	-----	-----	—	—

As indicated by the sponsor on 07/02/97, the full-scale production batch size will be —. The above batches (— of a full-scale production batch size) were, therefore, considered as pilot batches.

A new validated radioimmunoassay (RIA) method (Report No. DD-94-061) which has not been reviewed previously was used for analyzing plasma TAA levels and the method was found acceptable as shown below:

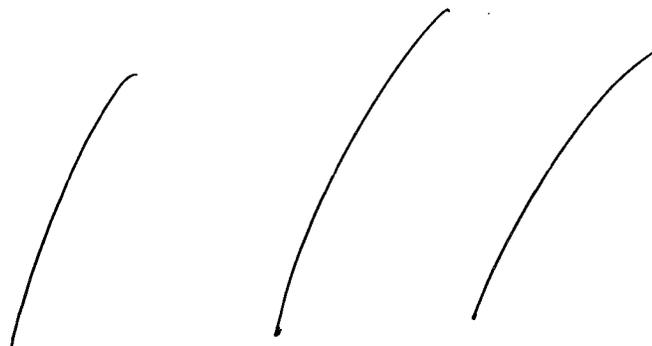
Standard Curve:

Accuracy:

Interday precision (CV%):

Intraday precision (CV%):

LOQ:



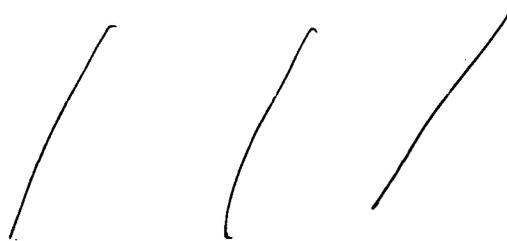
The results of QA are also summarized below:

Accuracy:

Interday precision (CV%):

Intraday precision (CV%):

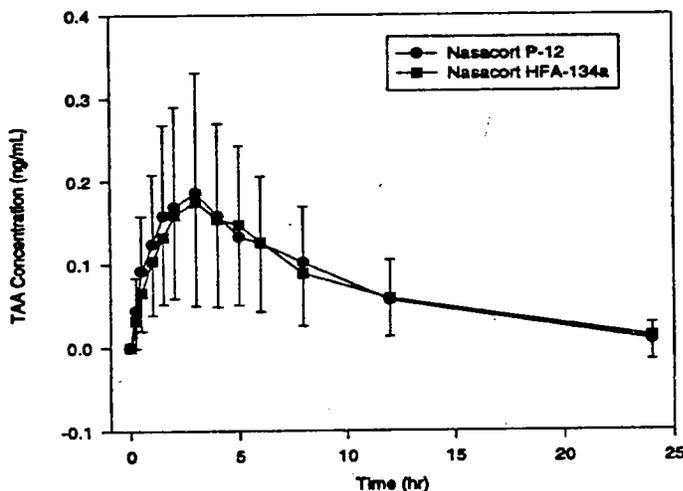
Crossreactivity:



Noncompartmental methods were used to calculate individual PK data/parameters. Statistical analysis was performed using GLM procedure within SAS and analysis of variance (ANOVA) for a 2-way crossover design was used at a 0.05 significant level. The Agency's two one-sided test procedures were performed and 90% confidence intervals (CIs) were used to assess BE between these two formulations for untransformed and log-transformed peak plasma level (C_{max}) and area under the plasma level-time curve (AUC) of TAA. Please see the dose administration, batch no., size, and date and site of manufacture of the formulations used, etc. in individual study report in Appendix 1 for details.

Mean plasma TAA levels obtained from the above BE study are shown below:

Figure 1:



Mean PK parameters and the results of the two one-sided tests for the BE assessment using untransformed C_{max} and AUC₀₋₁₂ are summarized below in Table 2:

Table 2:

Parameters (n = 23) ^a	Formulation A	Formulation B	Ratio ^b	90% Cis	Pass/Fail
C _{max} (ng/ml)	0.196 (58.1) ^c	0.205 (68.2)	96.7	82.1-111.3	Pass
T _{max} (hr)	3.8 ^d (63.8)	2.7 (47.7)	-----	-----	-----
AUC ₀₋₁₂ (ng-hr/ml)	1.31 (63.1)	1.36 (70.2)	97.6	83.5-111.7	Pass
T _{1/2} ^e (hr)	4.1	5.2	-----	-----	-----

- a. Subject # 13 was considered as a statistical outlier and excluded from analysis.
 b. The Ratio of A/B x 100%.
 c. Coefficient of Variation (CV%) calculated as SD/Mean x 100%.
 d. Significantly different from 2.7 hr (P < 0.05).
 e. Apparent terminal half-life (harmonic mean).

The results of the two one-sided tests for log-transformed C_{max} and AUC₀₋₁₂ values were not provided by the sponsor, however, they were calculated by this reviewer, 87.8-122.4 for C_{max} (pass) and 82.2-143.4 for AUC₀₋₁₂ (failed).

RECOMMENDATION:

The human PK/Bio section of NDA 20-784 for TAA that was submitted on 12/17/96 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the above two formulations are not BE based on the Agency's BE acceptance criteria for log-transformed AUC₀₋₁₂ value. The reviewing medical officer should, therefore, make a final decision on the approvability of the HFA formulation of Nasacort Nasal Inhaler, the subject of NDA 20-784. The General and Labeling comments of OCPB/DPE II are provided below. General Comment Nos. 6 and 7 and the Labeling Comment (pages 5 and 6) as appropriate need to be conveyed to the sponsor ASAP.

GENERAL COMMENTS: (Nos. 6 and 7 need to be sent to the sponsor)

1. Although the two formulations failed the BE test for log-transformed AUC₀₋₁₂ value, the HFA formulation gave lower mean C_{max} and AUC₀₋₁₂ values than the CFC formulation indicating that the HFA formulation had less absorption than the CFC formulation. In addition, the HFA formulation had smaller CV% than the CFC formulation.
2. Mean T_{max} value for the HFA formulation is 3.8 hr (with larger CV%) which is significantly different from the CFC formulation, 2.7 hr (with smaller CV%). Although the BE assessment is not required for this parameter according to the

current Agency's policy, the clinical consequence for the "presumed" slower absorption of the HFA formulation is not known.

3. According to the Agency's BE acceptance criteria, log-transformed $AUC_{0-\infty}$ value (instead of AUC_{0-12}) should be used for the BE assessment. The sponsor reported $AUC_{0-\infty}$ values were 2.10 (\pm 1.04; n = 18) and 2.26 (\pm 1.31; n = 18) ng-hr/ml for HFA and CFC formulations, respectively. The $AUC_{12-\infty}$ (area from time 12 hr to infinity by extrapolation) values represent 38% and 40% of total AUC values, respectively. Ideally, it should represent no greater than 10 % of total AUC value. It was noted that only 4-6 subjects had detectable TAA plasma levels at 24 hr post dosing which made the assessment of $AUC_{0-\infty}$ difficult, therefore, $AUC_{0-\infty}$ values were not employed in this study.
4. It is to bring to the reviewing medical officer's attention that subject #13 whom was described as a statistical outlier by the sponsor was excluded from the BE assessment. Close examination of his TAA plasma levels showed that this subject had the highest plasma TAA levels between 0.25 and 12 hr postdosing for the treatment phase of HFA formulation. His C_{max} value was — .1g/ml at 2 hr postdoing. The sponsor indicated that 1) no potential cause for the large increase in his TAA plasma levels was suggested after reviewing his case report form and 2) no significant adverse experiences by body system and intensity for each treatment were found. As reported, to induce the maximum suppression of endogenous hydrocortisone levels by TAA is 3-4 ng/ml (Derendorf et al, Clin. Pharmacol. Ther. 1986; 39:313-317). Therefore, the above incidence may be less of a safety concern for this study.
5. Three comments from Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II were conveyed to the sponsor. On 07/02/97, the sponsor answered two of the three comments through the CSO, i.e., 1) the PK Study No. RG5029T-124 has never been conducted and 2) the actual batch sizes manufactured for the two formulations used in Study No. RG5029T-123 were in pilot scale (— of a full-scale production batch size). Last comment regarding the update/revision of the PI. The sponsor indicated that above three comments will be responded officially when the revised PK is submitted to the Agency.
6. In your study protocol, it was stated that all boxes, medication containers, unused study medication, and materials will be accounted for and returned to Rhône-Poulenc Rorer at the completion of the study (Volume 20, page 6-1-232). According CFR21 Part 320.63, it is stated that if the bioequivalence study is performed under contract, the contract research organization shall retain appropriately identified reserve samples of the test and reference formulations. Each reserve sample shall consist of a sufficient quantity to permit FDA to perform 5 times all the release tests required in the application

and shall be retained for a period of at least 5 years following the date of which the application is approved. Therefore, it is recommended that for future bioequivalence studies, the test and reference formulations be retained at the study site and the Agency's regulations be followed.

7. It is recommended that for the test and reference formulations to be used in a bioequivalence study, at least of a full-scale production batch size that is manufactured at commercial site(s) be used.

LABELING COMMENT: (Needs to be sent to the sponsor)

It is recommended that under Clinical Pharmacology section of the package insert,



07/02/97

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD/FT initialed by Dale P. Conner, Pharm.D. DPK 7/3/97

cc: NDA 20-784, HFD-570 (Honig, Barnes), HFD-870 (M.L. Chen, D. Conner, T.M. Chen), CDR (B. Murphy).

NDA 20-784 (Nasacort HFA Nasal Inhaler;
Triamcinolone Acetonide 55 μ g/actuation)

Appendix 1:

Individual Study Report

Study No. RG5029T-123

Title: " An Open-Label, Randomized PK Comparison of Nasacort Nasal Inhaler/CFC Propellant and Nasacort Nasal Inhaler/134a Non-CFC Propellant in Healthy Adult Male Subjects"

Investigator and Study Site:

The study was conducted by _____

Objective:

To assess BE between the new Nasacort formulation with HFA-134a propellant and currently marketed Nasacort formulation with CFC-P12 propellant.

Study Design:

This was an open-label, randomized, 2x2 crossover, single-dose PK study with a washout period of 1 wk.

Population:

Twenty four healthy male volunteers were enrolled and completed the study. Their mean (\pm SD) age, BW, and height are 25.9 (\pm 8.2) years old, 169 (\pm 20) lb, and 71.2 (\pm 2.2) in, respectively.

Formulation, Dosage, and Administration:

The new to-be-marketed Nasacort formulation with HFA-134a propellant (Formulation A) and the currently marketed Nasacort formulation with CFC-P12 propellant (Formulation B) were used and they are summarized below. Detailed information on the formulations used is summarized in Appendix 2.

Formulation\Lot	Number	Size ^a	Date of Manufacture
A. Nasacort/HFA-134/a	5029/15-21A-1		09/07/93
B. Nasacort/CFC-P12	5029/15-22A-1		05/13/93

^a As indicated by the sponsor on 07/02/97, the full-scale production batch size will be _____

Subjects reported to the investigation site on the evening of Day 1 and were fasted overnight at 10:00 pm. On Day 2 morning, the subjects received assigned medication (4 x 55 µg per nostril of either formulation A or B). A total single dose of 440 µg was given. A standard breakfast was given 2 hr post dosing and lunch and dinner were served at any convenient time thereafter. Subjects were released after completion of 12th hr blood sampling and were instructed to come back next morning for the 24th hr blood sample.

Sample Collection:

Venous blood samples (≈ 10 ml each) were collected at baseline (time zero), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hr postdosing (n=13). Samples were centrifuged at -4°C within 10 min of collection. Plasma was harvested and 2 aliquots of 2 ml plasma were stored frozen at -20°C until assay.

Assays:

Plasma TAA levels were analyzed in the Clinical Drug Disposition Department of RPR using a validated RIA method (Report No. DD-94-061) which has never been submitted previously under NDA 19-798 for review. The RIA method has been validated by — and was transferred to RPR . The results of assay validation are summarized below:

Standard Curve:

Accuracy:

Interday precision (CV%):

Intraday precision (CV%):

LOQ:

The results of QA are summarized below:

Accuracy:

Interday precision (CV%):

Intraday precision (CV%):

Crossreactivity:

Data Analyses:

Noncompartmental methods were used to calculate individual PK data/parameters. Statistical analysis was performed using GLM procedure within SAS and ANOVA for a 2-way crossover design was used at a 0.05 significant level. Ninety % CIs were calculated for both nontransformed and log-transformed C_{max} and AUC_{0-12} values.

Results:

The individual plasma TAA levels were spot checked and they were found acceptable. For study results, please see PK summary of this bioreview for details.

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NDA 20-784 (Nasacort HFA Nasal Inhaler;
Triamcinolone Acetonide 55 μ g/actuation)

Appendix 2:

Proposed Package Insert (Dec. 17, 1997
Version) and Batch No., Size, and Date of
Manufacture of the Formulations used, etc.

18 Page(s) Withheld

 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process