

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-120

ADMINISTRATIVE DOCUMENTS

Memorandum

To: NDA 20-120, Tri-Nasal Spray
From: Hilary V. Sheevers - Pharm./Tox. Team Leader
Re: Team Leader NDA Summary, HFD 570
Date: September 12, 1996

1/5/96
9/13/96

NDA 20-120 is for Tri-nasal Spray, an intranasal formulation of the glucocorticoid triamcinolone acetonide nasal solution (0.05%) The proposed indications for Tri-nasal Spray are for the treatment of seasonal and perennial rhinitis symptoms. Patients are expected to be greater than 12 years old, and the maximum dose is 400 µg/day. The innovator products for Tri-Nasal Spray is Nasacort (Rhone-Polenc Rorer, RPR). This NDA (20-120) appears to be covered by FD&C Act 505 (b)(2), and thus does not represent an innovator product and makes use of data generated under Nasacort.

[

A large set of preclinical studies were performed for Nasacort. In rats and dogs, triamcinolone is rapidly metabolized to 3 products; the metabolites are expected to have significantly less activity than the parent compound. Several inhalation and/or intranasal studies were performed for earlier NDAs, including a 76-week inhalation study in monkeys and a 26 week study in rats. Because these studies were performed at a much earlier date, they do not include a number of items that we would expect to see in recently performed studies, such as PK and 7 day/week dosing regimens. The chronic studies were performed under GLP, however, and previously accepted as adequate. The toxicity profiles revealed findings as expected for a steroid, including changes in the target organs such as the adrenals, liver, thymus, and spleen. Immunosuppressive effects such as bacterial infections, suppurative inflammatory reactions, and lymphopenia were also noted. The most up-to-date intranasal study, which included PK data, was a 4 week study performed in dogs. Treatment related changes were noted in the thymus, spleen, adrenals, and the liver; and included atrophy of the thymus and lymph nodes, and adrenal cortical vacuolation at AUC values of approximately 0.78 ng.hr/ml (AUC in healthy males = 0.10 ng.hr/ml following a dose of 240 µg). No NOAEL was noted in the dog. Although several of the chronic studies are outmoded, the studies combined indicate that trimacinolone causes classic steroid effects and no unexpected toxicity.

Reproduction studies were performed in the rat to test impairment of fertility (Segment I) and multi-generational reproductive effects (Segment III), and in rats, rabbits and monkeys to test for teratogenicity (Segment II). Oral triamcinolone did not impair fertility in males or females,

although dystocia, prolonged delivery, increased resorptions, stillbirths, decreased pup weight and decreased pup survival were noted at doses below the clinical dose on a $\mu\text{g}/\text{kg}$ basis (7-16% of the clinical dose). These findings are consistent with expected reproductive effects of steroids. Additionally, the studies were performed orally, and we may expect the nasal formulations to reach lower systemic levels than seen with oral studies. (No PK data was collected in these older studies, and thus blood level comparisons cannot be made.) Segment II teratology studies were performed with inhalation formulations. In rats and rabbits, and at doses approximately equal to the clinical dose on a $\mu\text{g}/\text{kg}$ basis, cleft palate, hydrocephaly, and axial skeletal defects were noted. In monkeys at doses 20 times the human dose, CNS and cranial malformations were noted.

Two oral carcinogenicity studies were performed. In the albino mouse, triamcinolone was given at 0.1, 0.6, and 3.0 $\mu\text{g}/\text{kg}$ for 104 weeks. A slight but significant increase in lymphomas was noted in high-dose females. In treated males, an increased number of bronchoalveolar adenomas and carcinomas were noted, although the increase was not statistically significant. The findings do not appear to be biologically relevant and are not of significant concern. In the albino rat, triamcinolone was given at doses of 0.05, 0.02, and 1.0 $\mu\text{g}/\text{kg}$ for 104 weeks. These dose levels corresponded to 32, 135, and 712 pg.eq/ml when evaluated in plasma at week 59. An increased number of pituitary and adrenal medullary tumors were noted in treated animals, but the increase was not statistically significant and are not considered to be of concern. Note that these oral studies were performed at doses lower than what would be expected with today's standards, and are also at doses below the clinical dose. No mutagenicity studies were performed for triamcinolone.

Labeling changes are noted in detail in the pharmacology review. The changes were made to reflect recent language conformities and to quantify the 5-fold increase in serum values noted in human PK studies. Of note for the labeling changes is that most of the clinical comparisons of concern (such as carcinogenicity and reproduction studies) are now approximately equal to or much less than the clinical dose.

It is my understanding that the acceptability of these studies and the lack of mutagenicity data were addressed in earlier discussions with the company and the Agency, and we agreed to accept the data as it exists. Based on these agreements, the submission is recommended to be approvable.

Attachment.

**APPEARS THIS WAY
ON ORIGINAL**

cc: ~~ASA~~ 20-120

Dir File

HFD 570 Sheevers

HFD 570 Whitehurst

HFD 570 Barnes

WITHHOLD 5 PAGE (S)

Division Director's Memorandum

Date: Thursday, February 03, 2000
NDA: 20-120
Sponsor: Muro
Proprietary Name: Tri-Nasal Spray

From: Robert J. Meyer, MD *RS*
Director, Division of Pulmonary and Allergy Drug Products

Introduction: See Dr. Jenkins' memorandum of 9-19-96 for details. This is a 505(b)(2) NDA for triamcinolone nasal spray (referring to the Nasalcort Nasal Aerosol product) submitted originally prior to PDUFA-I, in Jan. 1992. It has gone through multiple review cycles, the latest of which was largely to resolve some substantive CMC issues, which now have been addressed adequately. This application is over its regulatory due date because of delays in getting updated inspections, however, there are now acceptable EERs.

CMC: All issues have been satisfactorily resolved to the point of allowing marketing. There is one CMC-related phase 4 commitment for _____ The company has committed to these and will submit a post-marketing report within 3 months of approval. There is also a CMC-Toxicology issue with _____ In order to support a level _____ in the drug product, the sponsor commits to conducting two genotoxicity assays and submitting the results by 6 months following approval.

Clinical / Stastical: Due to the concerns about corticosteroids and their effects on growth, the class-labeling for the intranasal corticosteroids will be included in the FPL and a phase 4 commitment was made to conduct a growth study and to report this study within 3 years. Other pediatric data do not appear to be required (although they would be useful), since the 1999 Pediatric Rule does not apply to this application by the criteria laid out in 21 CFR 314.55 (i.e., this NDA is not for a new chemical entity, a new dosage form, or a new route of administration).

Conclusions: This NDA can be approved once final labeling is received from the sponsor. The three phase-4 commitments have been agreed to in writing by the sponsor.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DATE: September 19, 1996

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products

TO: NDA 21-120

SUBJECT: Overview of NDA Review Issues

ISI
9/19/96

Administrative

NDA 20-120 for Tri-Nasal (triamcinolone acetonide) Spray was originally submitted by Muro Pharmaceutical, Inc. January 17, 1992. The application was submitted as a 505(b)(2) application with Nasacort Nasal Inhaler as the approved reference product. There is currently a use patent held by Rhone Poulenc Rorer for Nasacort Nasal Inhaler listed in the FDA Orange Book with a January 23, 2007 expiration date. Muro submitted a paragraph IV certification to the patent and provided proper notification to RPR on April 5, 1996. RPR did not respond to this notification within the required 45 day waiting period, therefore, there is no patent issue standing in the way of FDA approval of the Tri-Nasal application

The NDA was originally reviewed in HFD-007 and the sponsor received a Not Approvable letter on August 14, 1992. The Not Approvable letter listed Clinical, Biopharmaceutics, Preclinical, and CMC deficiencies, but did not constitute a complete listing of all deficiencies as the application was submitted prior to implementation of the User Fee Program. The application was resubmitted by Muro on October 31, 1996 and was reviewed by HFD-570 since the intranasal and inhaled corticosteroid products were transferred to the Division of Pulmonary Drug Products in April 1994. The sponsor submitted a major amendment to the application on July 1, 1996 which extended the regulatory due date to September 17, 1996 (NOTE: The action letter for this application was issued on September 17, 1996, this memorandum summarizing the review issues was completed after the issuance of the action letter).

Clinical

For a more detailed assessment of the clinical review of this NDA, please refer to the review written by Dr. Saavedra-Delgado and the medical supervisor's memorandum written by Dr. Himmel on August 21, 1996. The sponsor submitted 4 adequate and well-controlled trials evaluating the efficacy of Tri-Nasal at total doses of 50-400 mcg per day administered either once or twice daily in patients with seasonal allergic rhinitis (SAR). Overall these studies demonstrated that daily doses of Tri-Nasal of 200 and 400 mcg were consistently superior to placebo in relieving the nasal symptoms of SAR; the 50 mcg dose was not consistently superior to placebo. The sponsor did not provide any adequate and well-controlled clinical trials in perennial allergic rhinitis (PAR) that demonstrated Tri-Nasal to be superior to placebo. The study submitted by the sponsor to support a topical effect of Tri-Nasal was inadequate to accomplish its objectives since the intra-nasal dose of Tri-Nasal produced greater systemic

exposure to triamcinalone than the intra-muscular formulation used as the comparator.

The primary safety issue for Tri-Nasal results from the fact that triamcinolone is more systemically available when administered as Tri-Nasal than when administered as Nasacort Nasal Inhaler. The sponsor conducted a 6 week clinical trial to assess the impact of Tri-Nasal on the HPA axis using cosyntropin stimulation at baseline and Day 43. In this small study, no effect on the HPA axis was observed for the 400 mcg/day dose. While the active control of prednisone was not statistically significantly different from placebo in this small trial, there was a strong numerical trend demonstrating the expected suppression of HPA response to cosyntropin challenge. There was also a numerical ordering of effect on the HPA response to higher doses of Tri-Nasal (800 and 1600 mcg/day). These results support the safety of the 400 mcg maximum proposed daily dose for Tri-Nasal and should be reflected in the labeling. As detailed in Dr. Himmel's memo, there are additional published data for Nasacort AQ which supports the safety of the systemic exposures seen with Tri-Nasal at daily doses of 400 mcg.

The vast majority of patients studied in the NDA were 18 years of age or greater. Based on a limited number of patients between 12 and 18 years of age exposed to Tri-Nasal in the NDA, the Agency's conclusion that Tri-Nasal was safe and effective in the population studied in the NDA, and the fact that the approved reference product (Nasacort Nasal Inhaler) is approved for use in patients 12 years of age and greater, Tri-Nasal Spray is clinically approvable for the treatment of SAR in patients 12 years of age and greater. As noted above, the sponsor did not provide any adequate and well-controlled trials to demonstrate the safety and efficacy of Tri-Nasal in patients with PAR. The approved reference product, Nasacort Nasal Inhaler, is approved for PAR.

[Since triamcinolone is known to work in SAR and PAR, the sponsor has demonstrated Tri-Nasal to be safe and effective in SAR, and since the sponsor has adequately addressed the safety concerns related to Tri-Nasal's higher systemic bioavailability, Tri-Nasal Spray is clinically approvable for treatment of PAR in patients 12 years of age and greater.]

Preclinical

The sponsor did not submit any preclinical studies to this NDA, therefore, this 505(b)(2) application relies on the Agency's finding of safety and efficacy of the approved reference product, Nasacort Nasal Inhaler. There are no new excipients in the Tri-Nasal Spray or other issues that serve to invalidate the application of the Agency's finding of safety and efficacy of Nasacort to Tri-Nasal.

The application is approvable from a pre-clinical standpoint with labeling modeled after the approved Nasacort Nasal Inhaler labeling.

CMC

Tri-Nasal Spray is a metered dose pump spray solution formulation of triamcinolone acetonide for nasal application. Each spray delivers 50 mcg of triamcinolone acetonide. There

are numerous outstanding CMC deficiencies as identified in Dr. Ng's review.

The application is not approvable from a CMC standpoint and the CMC deficiencies will be included in the action letter to the sponsor.

Biopharmaceutics

The primary biopharmaceutics issue for this application is the fact that Tri-Nasal is more systemically bioavailable than Nasacort Nasal Inhaler. Triamcinolone is rapidly absorbed following intranasal application of Tri-Nasal as indicated by a shorter T_{max} (0.47 hr for Tri-Nasal vs 2.28 hr for Nasacort). Statistically significantly higher C_{max} and AUC were obtained with Tri-Nasal than with Nasacort. Studies conducted by the sponsor also demonstrated that the dose normalized PK parameters increase less than proportionally with increasing doses of Tri-Nasal between 100 and 400 mcg. The increased bioavailability of Tri-Nasal raises systemic safety issues which are addressed under the clinical review.

The application is approvable from a biopharmaceutics standpoint provided there are adequate clinical data to support the safety of the increased systemic bioavailability.

Data Integrity

The Division did not request clinical site audits be conducted by the Division of Scientific Investigations for this application since the product was not a new molecular entity and the Division had access to a large database on the safety and efficacy of triamcinolone nasal spray.

Summary

There are numerous CMC deficiencies that must be corrected prior to approval of this NDA. Given the nature of the deficiencies and the time likely to be required to develop and validate methods and to generate data to respond to the issues, the Division has decided that the action letter will be NOT APPROVABLE. The application is, however, approvable from the standpoint of other disciplines for an indication for treatment of SAR and PAR in patients 12 years of age and greater provided acceptable labeling is submitted by the sponsor. Preliminary labeling comments will be included in the action letter.

cc:

HFD-570/Division Files

HFD-570/Jenkins

HFD-570/Himmel

HFD-570/Barnes

HFD-570/Schumaker

**APPEARS THIS WAY
ON ORIGINAL**

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST



NDA # 20-120 Drug: TriNasal (triamcinolone acetonide)
 Applicant: Muro Chem/Ther/other Types: _____
 CSO/PM: Barnes Phone: 7-1075 HFD- 570
 Dne Date Sept 17 USER-FEE GOAL DATE: Sept 17 DATE CHECKLIST COMPLETED: _____

Arrange package in the following order (include a completed copy of this CHECKLIST): _____ Check or Comment _____

1. ACTION LETTER with supervisory signatures
 Are there any Phase 4 commitments? AP _____ AE _____ NA
 No Yes _____

2. Have all disciplines completed their reviews?
 No Yes _____
 If no, what review(s) is/are still in draft?
chem rev

3. LABELING (package insert and carton and container labels).
 (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)
 Draft _____
 Revised Draft _____
 Final _____

- 4. PATENT INFORMATION
- 5. EXCLUSIVITY CHECKLIST
- 6. PEDIATRIC PAGE (all NDAs)
- 7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).

NOT NEEDED
NOT NEEDED
NOT NEEDED but still submitted copy in pkg
NOT Requested
See E Mail in pkg

8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES
 If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
 If no audits were requested, include a memo explaining why.

9. REVIEWS & MEMORANDA:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	_____
GROUP LEADER'S MEMO	1 discipline, separate reviews	<input checked="" type="checkbox"/> _____
MEDICAL REVIEW	with a sheet of colored paper.	<input checked="" type="checkbox"/> _____
SAFETY UPDATE REVIEW	Any conflicts between reviews	_____
STATISTICAL REVIEW	must have resolution documented	<input checked="" type="checkbox"/> _____
BIOPHARMACEUTICS REVIEW		<input checked="" type="checkbox"/> _____
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		<input checked="" type="checkbox"/> _____
Statistical Review of Carcinogenicity Study(ies)		_____
CAC Report/Minutes		_____
CHEMISTRY REVIEW		_____
Labeling and Nomenclature Committee Review Memorandum		<input checked="" type="checkbox"/> _____
Date EER completed <u>8/21/96</u> (attach signed form or CIRTS printout)		OK <input checked="" type="checkbox"/> No _____
FUR needed _____ FUR requested _____		_____
Have the methods been validated?		Yes (attach) _____ No <input checked="" type="checkbox"/> _____
Environmental Assessment Review / FONSI	<u>Deficiencies in letter</u>	Review _____ FONSI _____
MICROBIOLOGY REVIEW		_____
What is the status of the monograph?		_____

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes
 11. MINUTES OF MEETINGS

NONE

Date of End-of-Phase 2 Meeting: _____
 Date of pre-NDA Meeting: _____

12. ADVISORY COMMITTEE MEETING MINUTES
 or, if not available, 48-Hour Info Alert or pertinent section of transcript.
 Minutes _____ Info Alert _____
 Transcript _____ No mtg

13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS
NONE
 14. If approval letter, has ADVERTISING MATERIAL been reviewed?
 Yes _____ No _____
 Yes, documentation attached _____
 No, included in AP ltr _____

15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA) NOT NEEDED

16. INTEGRATED SUMMARY OF SAFETY (from NDA) NOT NEEDED

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20120</u>	Trade Name:	<u>TRINASAL NASAL SOLUTION</u>
Supplement Number:		Generic Name:	<u>TRIAMCINOLONE ACETONIDE</u>
Supplement Type:		Dosage Form:	<u>Aerosol; Nasal</u>
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 12 years of age or older</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

<input type="checkbox"/> NeoNates (0-30 Days)	<input type="checkbox"/> Children (25 Months-12 years)
<input type="checkbox"/> Infants (1-24 Months)	<input type="checkbox"/> Adolescents (13-16 Years)
<input checked="" type="checkbox"/> Other Age Groups (listed): <u>12 years and older</u>	

Label Adequacy	<u>Adequate for SOME pediatric age groups</u>
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

P4 commitment to study effects on growth in prepubertal children

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DAVID HILFIKER

Signature DS

Date 1/27/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0916-0001
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT MURO PHARMACEUTICAL, INC.	DATE OF SUBMISSION 7/1/96
ADDRESS (Number, Street, City, State and ZIP Code) 890 East Street Tewksbury, MA 01876	TELEPHONE NO. (Include Area Code) (508) 851-5981
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued) 20-120

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN) Triamcinolone acetate nasal solution 0.05%	PROPRIETARY NAME (if any) Tri-nasal Spray
---	--

CODE NAME (if any) N/A	CHEMICAL NAME 9-Fluoro-11 β ,16 α ,17,21-tetrahydroxy pregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone
---------------------------	--

DOSAGE FORM Solution	ROUTE OF ADMINISTRATION Nasal	STRENGTH(S) 0.05%
-------------------------	----------------------------------	----------------------

PROPOSED INDICATIONS FOR USE
For the treatment of seasonal and perennial allergic rhinitis symptoms

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:



INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
--------------	--------------------------------

TYPE SUBMISSION (Check one)

PRE SUBMISSION AN AMENDMENT TO A PENDING APPLICATION SUPPLEMENTAL APPLICATION
 ORIGINAL APPLICATION RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) 21 CFR 314.60

PROPOSED MARKETING STATUS (Check one)

APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

Basis for 505 (b)(2) Submission

At a March 9, 1995 FDA/Muro pre-NDA conference, the Pulmonary Division CSO, Sandy Barnes, informed Muro that the Tri-Nasal application will be considered a 505 (b)(2) submission. Through this application process, Muro, as the sponsor, can reference another Company's NDA (listed drug) to rely on that drug's underlying safety and efficacy data without the innovating Company's permission.

Muro's drug is a new dosage form of the approved drug Nasacort®, whose application also references the approved drug Azmacort®. Since approval of our drug is based on clinical studies other than bioavailability/bioequivalency studies, the 505 (b)(2) route can only be used since an ANDA is not an option.

Muro identifies the listed drug for which the FDA has made a finding of safety and efficacy, and on which finding Muro relies in seeking approval for Tri-Nasal, as follows:

	<u>Listed Drug</u>
Established Name:	Triamcinolone Acetonide Nasal Aerosol -
Proprietary Name:	Nasacort®
Dosage Form:	Aerosol, Metered; Nasal
Strength:	0.055 MG/Inhalation
Route of Administration:	Nasal
Application Holder:	Rhone Poulenc Rorer
Approved NDA #:	19-798
Approval Date:	July 11, 1991

The FDA has agreed that Muro need not conduct carcinogenicity or toxicology studies for the Market Approval of Muro's Tri-Nasal solution since this data can be referenced in the listed drug's application. Therefore, Section 5 (Non-Clinical Pharmacology and Toxicology Section) is not included in the NDA submission.

Patent Information and Patent Certification

The application for Tri-Nasal Spray is subject to patent restrictions and, as a 505 (b)(2) submission requires certification statements similar to those found in both Full NDA's and Abbreviated NDA's.

Below are the required statements of patent certification (Paragraph II and IV) for Muro Pharmaceutical's New Drug Application #20-120 for Tri-Nasal Spray (triamcinolone acetonide nasal solution, 0.05%).

FDA PATENT CERTIFICATIONS

Pursuant to 21 C.F.R. Section 314.50(i)(1)(i)(A)(2) and (i)(1)(iii)(B), Muro Pharmaceutical, Inc. hereby certifies that in its opinion and to the best of its knowledge, the following are true with respect to the patents identified below:

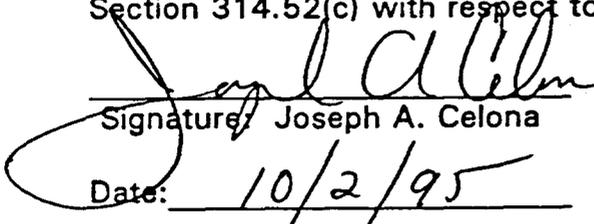
1) Paragraph II Certification:

Patent No. 4,048,310, for Triamcinolone Acetonide: Kenalog-H, expired September 13, 1994, as listed in the 1994 FDA "Orange Book."

2) Paragraph IV Certification:

I, Joseph A. Celona, certify that Patent No. 4,767,612 (the "'612 patent"), for Triamcinolone Acetonide: Nasacort, will not be infringed by the manufacture, use, or sale of the drug for which this application is being submitted.

Muro Pharmaceutical, Inc. will comply with the requirements under Section 314.52(a) of the FDA's rules with respect to providing notice to each owner of the '612 patent or their representatives and to the holder of the approved application for the drug product which is claimed by the '612 patent or a use of which is claimed by the '612 patent and with the requirements under Section 314.52(c) with respect to the content of such notice.


Signature: Joseph A. Celona

Date: 10/2/95

Joseph A. Celona

Typed Name

Director of Regulatory Affairs

Title

New Drug Product Exclusivity

Muro Pharmaceutical is claiming a three year period of Market Exclusivity for Tri-Nasal Spray. Muro believes its drug product is entitled to the period of exclusivity based on 21 CFR 314.108 (b)(4):

- (1) The application contains "new clinical investigation."

Muro certifies that to the best of Muro's knowledge, each of the clinical investigations included in the application meet the definition of "new clinical investigation" as set forth in 21 CFR 314.108 (a).

- (2) These new clinical investigations are "essential" to the approval of the application.

Attached is a list of all published studies and publicly available reports of clinical investigations known to Muro through a literature search that are relevant to the conditions for which Muro is seeking approval.

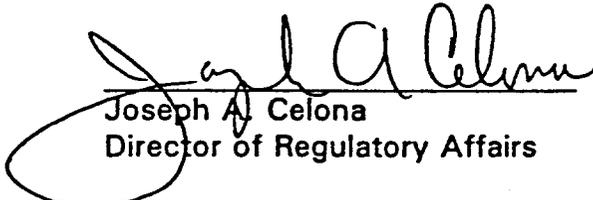
Muro certifies that we have thoroughly searched the scientific literature, and, to the best of Muro's knowledge, the list is complete and accurate, and, in Muro's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Muro is seeking approval without reference to the new clinical investigations in the application.

We can explain as to why the studies or reports are insufficient by the fact that FDA, in the not approved letter dated August 14, 1992, required these studies with our drug product for approval.

- (3) These new clinical investigations which were essential to approval, were sponsored by Muro Pharmaceutical, Inc. as stated in the Form FDA 1571, IND _____

Certified by,

Date: 10/2/95


Joseph A. Celona
Director of Regulatory Affairs

1 MEZZ

AI Settiple-G, Korenblat-P-E, Winder-J, Lumry-W, Murphree-J, Alderfer-V-B, Simpson-B, Smith-J-A.
 TI Triamcinolone acetonide Aqueous nasal spray in patients with seasonal allergic rhinitis: a placebo-controlled, double-blind study.
 SO Clin-Ther 1995 Mar-Apr, VOL: 17 (2), P: 252-63, ISSN: 0149-2918.
 AB Because some patients may prefer aqueous nasal sprays and once-daily dosing for relief of seasonal allergic rhinitis symptoms, a new aqueous formulation of triamcinolone acetonide (TAA Aqueous) was developed. We conducted a randomized, placebo-controlled, double-blind study to compare the efficacy and safety of once-daily administration of 220 micrograms/d of TAA Aqueous for 1 week, followed by either 220 micrograms/d or 110 micrograms/d for an additional 2 weeks, with that of placebo in 426 patients with seasonal allergic rhinitis. Patients recorded the severity of symptoms (nasal stuffiness, discharge, sneezing, nasal index (the sum of the first three variables), nasal itching, and eye symptoms) on daily diary cards. Patients' and physicians' global evaluations of efficacy were made at the end of the 3-week study period. Both regimens of TAA Aqueous significantly improved symptoms compared with placebo at most time points. Patients demonstrated significant improvements in nasal symptoms as early as the first day of treatment (within 12 to 16 hours based on treatment in the morning and symptom assessment at bedtime). Although TAA Aqueous 220 micrograms/d provided numerically greater reductions in nasal symptoms compared with 110 micrograms/d, these differences in efficacy over the last 2 weeks were not statistically significant. The incidence of adverse effects with both TAA Aqueous regimens was low and comparable to that of placebo. In summary, during the first week of therapy, TAA Aqueous 220 micrograms/d significantly reduced nasal symptoms. During the last 2 weeks of therapy, the 110 micrograms/d regimen of TAA Aqueous was effective as continued therapy for most patients. Both the 110 micrograms/d and 220 micrograms/d regimens of TAA Aqueous provided significantly better relief of nasal symptoms than did placebo. Author.

2 MEZZ

AU Wood-R-A, Eggleston-P-A.
 TI The effects of intranasal steroids on nasal and pulmonary responses to cat exposure.
 SO Am-J-Respir-Crit-Care-Med 1995 Feb, VOL: 151 (2 Pt 1), P: 315-20, ISSN: 1073-449X.
 AB To test the hypothesis that nasal antiinflammatory treatment can modify both upper and lower airway responses to allergen exposure, 12 cat-allergic subjects underwent 1 h cat exposure challenges at baseline, with nasal occlusion, and after 1 wk of treatment with either intranasal triamcinolone acetonide or placebo in a double-blind crossover trial. Challenges were performed in a room containing two cats with airborne $Fal\ d\ 1$ levels ranging from 36 to 37,525 ng/m³. Overall, nasal symptoms were moderately reduced by treatment ($p = 0.06$), with the greatest reduction occurring in the first 15 and 30 min of the challenge ($p < 0.01$ and $p < 0.05$, respectively). Mean lower respiratory symptoms were also diminished by treatment ($p = 0.02$), although these effects were most evident during the last 15 min of the challenge. Maximum changes in FEV₁ were slightly reduced by the nasal therapy ($p = 0.07$), reaching statistical significance only at the 30-min intervals ($p < 0.05$). There were no significant differences in nasal histamine or TAME esterase levels. When challenges were repeated with nasal occlusion, no significant differences were detected in chest symptoms or FEV₁ changes. We conclude that treatment with an intranasal corticosteroid led to significant reductions in both upper and lower airway responses to intense cat exposure. Author.

3 MEZZ

AU Krespi-Y-P, Kurloff-D-B, Anor-M.
 TI Sarcoidosis of the sinonasal tract: a new staging system.
 SO Otolaryngol-Head-Neck-Surg 1995 Feb, VOL: 112 (2), P: 221-7, ISSN: 0194-5998 22 Refs.
 AB Sarcoidosis is a chronic multisystem granulomatous disease that has a predilection for pulmonary and upper respiratory tract involvement. Because the initial signs and symptoms of sarcoidosis may be identical to those of other forms of chronic sinonasal inflammatory disease, these patients will often first seek treatment from an otolaryngologist. We present a series of 28 patients whose primary symptoms was involvement of a sinonasal tract. A new staging system is proposed to categorize the severity and sites of involvement and to guide the aggressiveness of therapy. Sarcoidosis should be considered in the differential diagnosis of inflammatory sinonasal disease. Author.

4 MEZZ

AI Argenti-D, Colligon-I, Heald-D, Ziemniak-J.
 TI Nasal mucosal inflammation has no effect on the absorption of intranasal triamcinolone acetonide.
 SO J-Clin-Pharmacol 1994 Aug, VOL: 34 (8), P: 854-8, ISSN: 0091-2700.
 AB The potential for enhanced systemic absorption of intranasal triamcinolone acetonide was explored in patients with inflamed nasal mucosa. Twelve allergic rhinitis patients with documented nasal inflammation, and 12 healthy volunteers, each received a single, therapeutic, 400-micrograms dose of triamcinolone acetonide in each nostril. Blood was obtained at fixed time points after the dose, and plasma concentrations of triamcinolone acetonide were determined by radioimmunoassay. There were no statistically significant differences in any of the derived pharmacokinetic parameters (maximum plasma triamcinolone acetonide concentrations (C_{max}), time to maximum plasma triamcinolone concentrations (T_{max}), elimination half-life (t_{1/2}), and area under the plasma concentration-time curve (AUC₀₋₁₂) from 0 to 12 hours) between treatment groups. A once-a-day, chronic regimen (8 weeks) of triamcinolone acetonide was also administered to five patients with allergic rhinitis. Pharmacokinetic parameters were similar to the parameters derived from healthy volunteers after acute administration. There was no evidence of drug accumulation. The results of this study indicate that acute and chronic intranasal administration. The results of this study indicate that acute and chronic intranasal administration of therapeutic doses of triamcinolone acetonide to patients with inflamed nasal mucosa does not result in enhanced systemic drug absorption or accumulation. Author.

5 MEZZ

AU Welch-M-J, Bronsky-E, Findley-S, Pearman-D-S, Southern-D-L, Storms-W-W, Weakley-S.
 TI Long-term safety of triamcinolone acetonide nasal aerosol for the treatment of perennial allergic rhinitis.
 SO Clin-Ther 1994 Mar-Apr, VOL: 16 (2), P: 253-62, ISSN: 0149-2918.
 AB A 1-year, open-label extension of a 12-week, double-blind clinical trial was conducted to evaluate the long-term safety and efficacy of once-daily therapy with triamcinolone acetonide nasal aerosol (110, 220, or 440 micrograms) in 93 patients with perennial allergic rhinitis. All three doses of triamcinolone acetonide were associated with sustained improvement in allergic rhinitis symptoms over the course of 1 year, as evidenced by physicians' and patients' global evaluations, ratings of the nasal environment (appearance and color of the nasal mucosa, as well as the quality of nasal secretions), nasal eosinophil counts, and requirement for escape medication. Among patients who reported adverse clinical experiences, most were considered unrelated or remotely related to therapy. Few patients experienced nasal irritation or throat discomfort, and no serious adverse experiences were attributed to treatment. Among 6 patients who withdrew from the study because of adverse experiences, a possible drug relationship was cited in 2 individuals (1 with headache and 1 with nasal blood) and a remote relationship in 1 (with acne). No clinically meaningful changes in vital signs, physical examinations, or laboratory values were noted, and mean serum cortisol levels were not suppressed during long-term treatment. These findings demonstrate that both safety and efficacy are maintained during long-term once-daily therapy with triamcinolone acetonide nasal aerosol in patients with perennial allergic rhinitis. Author.

6 MEZZ

AU Welch-M-J.
 TI Topical nasal steroids for allergic rhinitis.
 SO West-J-Med 1993 Jun, VOL: 158 (6), P: 616-7, ISSN: 0093-0415

7 MEZZ

AU Mabry-R-L.
 TI Corticosteroids in the management of upper respiratory allergy: the emerging role of steroid nasal sprays.
 SO Otolaryngol-Head-Neck-Surg 1992 Dec, VOL: 107 (6 Pt 2), P: 855-9, discussion 859-60, ISSN: 0194-5998.
 AB Corticosteroids are undoubtedly the pharmacotherapeutic agents with the broadest application for the treatment of many types of rhinitis, not just those of atopic origin. However, this potent class of drugs also has the greatest potential for adverse effects and complications. Proper use requires that they be used only after failure of more conservative measures, at the smallest effective dose, for the shortest possible time, and preferably should be administered by the topical intranasal route. Topical corticosteroids, concentrated at the area involved, offer significant relief to patients with allergic rhinitis, and although only a relatively small amount of drug is taken up systemically, cautions for proper use are important. Topical steroids should be used only after accurate diagnosis. They must adequately contact the nasal mucosa, and patients should be properly instructed in their use and monitored for local and systemic side effects. Currently available topical preparations—dexamethasone, beclomethasone, flunisolide, and triamcinolone—have differing characteristics. The use of a preparation with a high margin of safety reduces the risk of undesirable systemic effects. Author.

8 MEZZ

AU Findlay-S, Huber-F, Garcia-J, Huang-L.
 TI Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis
 SO Ann-Allergy 1992 Mar, VOL: 68 (3), P: 228-32, ISSN: 0003-4738
 AB A 4-week, double-blind, parallel group study compared the safety and efficacy of once-a-day intranasal administration of triamcinolone acetonide (Nasacort) versus placebo in 304 patients (155 adult and 149 adolescent) with seasonal allergic rhinitis. Patients were randomized to receive triamcinolone acetonide (110, 220, or 440 microgram) or placebo once daily each morning. Daily rhinitis symptoms scores, weekly patient and physician global assessments, and weekly nasal eosinophil smears were obtained. In each triamcinolone acetonide group, significant (P less than .05) improvement over placebo was noted in the nasal index (sum of ratings for stuffiness, discharge, and sneezing) by week 1, the first point of analysis, and maintained throughout the study. Triamcinolone acetonide groups also demonstrated significant (P less than .05) improvement over placebo in all individual rhinitis symptoms evaluated. The greatest improvement in symptoms was observed at the 440 microgram dose. A significant decrease in eosinophil counts paralleled clinical improvement in all triamcinolone acetonide groups. Physicians and patients rated triamcinolone acetonide significantly (P less than .05) more effective than placebo. Responses of adult and adolescent patients were comparable. Adverse experiences, clinical laboratory values, and results of physical examinations were unremarkable and comparable between the triamcinolone acetonide and placebo groups. We conclude that triamcinolone acetonide is safe, well tolerated, and superior to placebo as a once-a-day treatment for seasonal allergic rhinitis. Author.

9 MEZZ

AU Mabry-R-L.
 TI Topical pharmacotherapy for allergic rhinitis: new agents.
 SO South-Med-J 1992 Feb, VOL: 85 (2), P: 149-54, ISSN: 0038-4348
 Refs.
 AB The advantages of topical (as opposed to systemic) therapy for allergic rhinitis include the avoidance of undesirable systemic effects and the concentration of therapeutic effect on the target organ. Successful topical therapy requires establishment of a proper diagnosis, followed by effective delivery of the medication to the nasal mucosa. In addition to currently available preparations such as cromolyn sodium and various corticosteroids, several other topical nasal preparations for the treatment of allergic rhinitis are under investigation. These include antihistamines (eg, levocabastine), anti-inflammatory/mast cell stabilizing drugs (eg, nedocromil), new corticosteroids (eg, triamcinolone, budesonide, flucortin, fluticasone), anticholinergics (eg, ipratropium), and miscellaneous agents (eg, HEPP (IgE pentapeptide)). Author.

10 MEZZ

AU Gemboa-P-M, Juregui-I, Antepar-I.
 TI Contact dermatitis from budesonide in a nasal spray without cross-reactivity to amcinonide.
 SO Contact-Dermatitis 1991 Mar, VOL: 24 (3), P: 227-8, ISSN: 0105-1873.

11 MEZZ

AU Welch-M-J, Bronsky-E-A, Grossman-J, Shapiro-G-G, Tinkelman-D-G, Garcia-J-D, Gillen-M-S.
 TI Clinical evaluation of triamcinolone acetonide nasal aerosol in children with perennial allergic rhinitis
 SO Ann-Allergy 1991 Nov, VOL: 67 (5), P: 493-8, ISSN: 0003-4738
 AB Triamcinolone acetonide aerosol (TAA), a topical corticosteroid, now available for intranasal use, has been shown to be highly effective in the treatment of both seasonal and perennial allergic rhinitis (PAR) in adults. To evaluate the efficacy and safety of TAA in children, 210 patients (ages 4 to 12 years) with PAR were randomly assigned to one of three treatment groups (placebo, TAA 82.5 micrograms/day, or TAA 165 micrograms/day). Medication was given bid over 12 weeks in a double-blind fashion. Response to medication was evaluated using symptom scoring, physician evaluation, and, in 44 patients, nasal airflow determinations by anterior rhinomanometry. The higher dose of TAA (165 micrograms/day) significantly improved rhinitis symptoms relative to placebo: the total nasal symptom score and most individual symptom scores (eg, nasal stuffiness, itch, sneezing) were significantly better, duration of rhinitis symptoms (hours per day) was significantly reduced, and nasal airflow in a subset of patients showed significant improvement. The lower dose of TAA (82.5 micrograms/day) was superior to placebo by the same parameters as the higher dose, but this improvement was not as consistently significant as the higher dose. There were no clinically significant adverse events, nasal irritation and epistaxis were rare with a similar incidence among treatment groups. In conclusion, TAA at 165 micrograms/day was effective in controlling the symptoms of PAR and in improving nasal airflow in pediatric patients; the lower dose (82.5 micrograms/day) was marginally effective. Both doses were safe and well-tolerated in the children studied. Author.

12 MEZZ

AU Storms-W, Bronsky-E, Findlay-S, Pearlman-D, Rosenberg-S, Shapiro-G, Southern-L, Tinkelman-D, Weakley-S, Welch-M, et al
 TI Once daily triamcinolone acetonide nasal spray is effective for the treatment of perennial allergic rhinitis (published erratum appears in Ann Allergy 1991 Jun; 66(6):457).
 SO Ann-Allergy 1991 Apr, VOL: 66 (4), P: 329-34, ISSN: 0003-4738
 AB A randomized, double-blind, placebo-controlled, parallel group study was conducted in 11 centers to evaluate the safety and efficacy of a once-a-day regimen of 110 micrograms, 220 micrograms, and 440 micrograms of triamcinolone acetonide intranasal aerosol versus placebo in relieving the symptoms of rhinitis in 305 adult and older pediatric patients with perennial allergic rhinitis. Nasal stuffiness, nasal discharge, sneezing, nasal itching and the nasal index (the sum of the mean scores of the first three symptoms) averaged over the first 6 weeks and second 6 weeks of the study were significantly reduced in patients who received the 220 micrograms/day and the 440 micrograms/day dosages. The 110 micrograms/day group had a reduction in these nasal symptoms, but only the sneezing and nasal index were significantly (P less than .05) better than placebo. During the last 6 weeks of the study, patients were allowed to take oral back-up medication for their nasal symptoms; all three groups receiving triamcinolone nasal aerosol took less back-up medication than did the placebo group. There were no significant adverse effects or laboratory abnormalities noted during this study. Intranasal triamcinolone acetonide 220 micrograms and 440 micrograms, used once-a-day for 12 weeks is clinically and statistically superior to placebo for the treatment of perennial allergic rhinitis. Author.

13 MEZZ

AU Spector-S, Bronsky-E, Chervinsky-P, Lotner-G, Koepke-J, Selner-J, Pearlman-D, Tinkelman-D, Weakley-S, Alderfer-V, et al
 TI Multicenter, double-blind, placebo-controlled trial of triamcinolone acetonide nasal aerosol in the treatment of perennial allergic rhinitis
 SO Ann-Allergy 1990 Mar, VOL: 64 (3), P: 300-5, ISSN: 0003-4738
 AB In a double-blind study involving 205 patients with perennial allergic rhinitis, statistically significantly greater symptomatic improvements were evident following the administration of 200 micrograms/day triamcinolone acetonide aerosol than following placebo. These improvements were evident as early as week 1 and were sustained throughout the 12-week study. They were accompanied by greater reductions in nasal eosinophils. Triamcinolone acetonide aerosol was well tolerated and had no effect on serum cortisol levels. Author.

14 MEZZ

AU Tinkelman-D, Falliers-C, Gross-G, Segal-A, Southern-L, Welch-M, Yeates-H, Gorder-J, Garcia-J
 TI Multicenter evaluation of triamcinolone acetonide nasal aerosol in the treatment of adult patients with seasonal allergic rhinitis.
 SO Ann-Allergy 1990 Feb, VOL: 64 (2 Pt 2), P: 234-40, ISSN: 0003-4738
 AB Triamcinolone acetonide aerosol inhalation therapy is effective for the prophylactic treatment of asthma. Recently, the delivery system for this preparation has been modified for use in allergic rhinitis. A total of 180 adult patients with symptomatic seasonal allergic rhinitis participated in this double-blind, placebo-controlled, multicenter trial. Patients received either placebo or approximately 25 mg per actuation of triamcinolone acetonide aerosol per nostril, qid, for 4 weeks. Each patient kept a daily diary rating rhinitis symptoms. Both the patient and the physician also gave global evaluations of drug efficacy. Of 166 evaluable patients, significant reductions were seen at week 1, week 2, and in the overall study evaluation of ratings for intensity (P less than .001) and duration (P less than .05) of various rhinitis symptoms such as nasal stuffiness, discharge, and sneezing in the group given triamcinolone acetonide. Superiority to placebo group was evident as early as day 1 and maintained throughout the study. Both patients and physicians rated triamcinolone acetonide as significantly more effective than placebo for the duration of the study (P less than .001). There was a marked reduction in nasal smear eosinophils in the triamcinolone acetonide group. There was no difference between groups in safety evaluations including no evidence of suppression of the adrenal axis and no evidence of fungal infection. This study demonstrates that triamcinolone acetonide in a dose of 25 micrograms per nostril, qid, is effective, well tolerated, and safe in reducing symptoms in adult patients with seasonal allergic rhinitis. Author.

15 MEZZ

AU Estele-F, Simons-R, Simons-K-J

TI Optimum pharmacological management of chronic rhinitis.

SO Drugs 1989 Aug, VOL: 36 (2), P: 313-31, ISSN: 0012-6667 203 Refs.

AB Pharmacological treatment of chronic rhinitis has greatly improved with the introduction of the relatively non-sedating H1-receptor antagonists such as terfenadine, astemizole, loratadine, and cetirizine, and the safe, highly efficacious topical glucocorticosteroids such as beclomethasone dipropionate, flunisolide, budesonide, flucortin butyl, and triamcinolone acetonide. In patients whose chief complaint is rhinorrhoea, topical ipratropium bromide may be of value. Patients whose major symptom is nasal congestion will benefit from intermittent use of topically or orally administered decongestants. In patients with allergic rhinitis, sodium cromoglycate (cromolyn sodium) or nedocromil sodium or used topically intranasally have a moderate beneficial effect and are associated with a low incidence of adverse effects. Non-pharmacological treatment of chronic rhinitis cannot be ignored. Patients must avoid inhalation of cigarette smoke and other irritants. Patients with chronic allergic rhinitis should avoid antigens to which they have known sensitivity; in addition, selected patients with allergic rhinitis may benefit from immunotherapy with the offending antigen(s). Author.

16 MEZZ

AU Wood-S-F.

TI Hay fever. 2. Clinical features, diagnosis, investigation and treatment.

SO Fam-Pract 1986 Jun, VOL: 3 (2), P: 120-5, ISSN: 0263-2136.

AB This is the second of two reviews of hay fever. The first article dealt with prevalence and natural history, historical background and mechanisms. This article outlines the clinical features of hay fever, examines the correlation of symptoms with pollen count and describes current views of diagnosis and investigation. History and examination, skin testing, the radio-immunosorbent test (RIST) and radio allergosorbent test (RAST) and the correlation between RAST and skin testing are described. Some consideration is given to the part played by nasal challenge tests and measurements of nasal airways resistance. The section on treatment includes some general considerations, avoidance measures, anti-histamines, nasal steroids, sodium cromoglycate, systemic steroids, nasal vasoconstrictors, hyposensitisation and eye preparations. The final section is centred on future developments. Author.

17 MEZZ

AU Nagai-T.

TI Topical mucosal adhesive dosage forms.

SO Med-Res-Rev 1986 Apr-Jun, VOL: 6 (2), P: 227-42, ISSN: 0198-6325 18 Refs.

18 MEZZ

AU Kusanagi-T

TI Epithelial changes of the nasal columella of the palatal slit and cleft palate defects in C57BL/6 mouse fetuses

SO Teratology 1985 Feb, VOL: 31 (1), P: 111-7, ISSN: 0040-3709.

AB Palatal slit and cleft palate are induced in fetuses of C57BL/6 female mice treated with triamcinolone acetonide. In this study, the progressive changes in the epithelia of the presumptive fusion areas of the nasal columella and the anterodorsal part of the secondary palate were examined histologically. No difference was seen in the epithelial changes of the nasal columella of fetuses with palatal slit and those with cleft palate. In the treated palates the basal cuboidal epithelial cells in the presumptive fusion area of the nasal columella extended further toward the nasal cavity, and the vacuolization of the nasal epithelial cells appeared earlier than in the untreated palates. Although the treatment produced epithelial changes of the presumptive fusion area, its primary effect does not seem to be the disturbance of the epithelial fusion processes. The induction of palatal slit may be due to a failure of the primary and secondary palates to make adequate contact and fuse at the appropriate developmental stage because the secondary palate closure is delayed. Author.

19 MEZZ

AU Clitsold-S-P, Heel-R-C

TI Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis.

SO Drugs 1984 Dec, VOL: 28 (6), P: 465-518, ISSN: 0012-6667 118 Refs.

AB Budesonide is a non-halogenated glucocorticosteroid which has been shown to possess a high ratio of topical to systemic activity compared with a number of reference corticosteroids such as beclomethasone dipropionate, flunisolide, and triamcinolone acetonide. It appears to undergo extensive first-pass metabolism to metabolites of minimal activity which accounts for the low level of systemic activity. The majority of therapeutic trials in asthma have been of short term duration and have demonstrated that conventional doses of inhaled budesonide (200 to 800 micrograms/day) and beclomethasone dipropionate (400 to 800 micrograms/day) are of similar efficacy in both adults and children with moderate to severe asthma. Other studies have compared high doses of inhaled budesonide (400 to 3200 micrograms/day in 4 divided doses) with both alternate day (7.5 to 60 mg) and daily (7.5 to 40 mg) oral prednisone in patients with severe or unstable asthma. In the small number of such trials to date, inhaled budesonide was superior to prednisone with respect to the level of asthma control and the lesser influence on adrenal function. Long term open studies have similarly shown that inhaled budesonide can be gradually substituted for oral prednisone in steroid-dependent patients, often with a concomitant improvement in pulmonary function and asthma control. Intranasal budesonide (200 to 400 micrograms/day) relieves nasal symptoms in patients with seasonal allergic, perennial allergic and vasomotor rhinitis. In comparative studies in patients with seasonal rhinitis it has been shown to be of similar efficacy as intranasal flunisolide and intranasal beclomethasone dipropionate and superior to intranasal sodium cromoglycate (cromolyn sodium) and the antihistamine dexchlorpheniramine. Following inhalation, the most commonly reported side effects have been candidiasis, dysphonia and sore throat, while after intranasal administration the most frequent adverse reactions have been nasal stinging, throat irritation, dry nose and slight nasal bleeding. At usual dosages, both formulations of budesonide appear to have little or no effect on adrenal function. Thus, at this stage in its development budesonide has been shown to offer an effective alternative to oral or other inhaled corticosteroids in the management of asthma and rhinitis. However, its relative efficacy and tolerability during long term use, compared with beclomethasone dipropionate, remains to be clarified. Author.

20 MEZZ

AU Meinick-M, Jaskoll-T, Marazita-M

TI Localization of H-2Kk in developing mouse palates using monoclonal antibody

SO J-Embryol-Exp-Morphol 1982 Aug, VOL: 70, P: 45-60, ISSN: 0022-0752

AB Using monoclonal antibodies to H-2Kk antigen, we sought to develop a reproducible method of *in situ* localization in embryonic tissue and to determine whether there are specific patterns of H-2 localization in time and space in the developing palatal tissues of B10 A(H-2a) embryonic mice, with and without corticosteroid pretreatment at 12 days gestation. Our procedure employs ethanol-glacial acetic acid fixation, paraplast embedding, and enzymatic predigestion with purified hyaluronidase and neuraminidase. H-2 antigens were detected in palatal mesenchyme as well as basement membranes but not in oral or nasal epithelium. The pattern of distribution in mesenchyme of untreated embryos changed with progressive shelf development: vertical leads to horizontal leads to epithelial fusion leads to epithelial seam degeneration leads to mesenchymal confluence. Although the palatal shelves of treated embryos remained vertical, corticosteroid treatment does not appear to alter the detectable spatiotemporal distribution of H-2 antigens in developing palates of embryonic B10 A mice. Author.

21 MEZZ

AU Meinick-M, Jaskoll-T, Slavkin-H-C

TI Corticosteroid-induced cleft lip in mice: a teratologic, topographic, and histologic investigation.

SO Am-J-Med-Genet 1981, VOL: 10 (4), P: 333-50, ISSN: 0148-7299

AB Unlike cleft palate, relatively few teratogens have been found to induce cleft lip in mice. The present study was designed to assess the teratologic, topographic (SEM), and histologic effects on lip morphogenesis following the administration of triamcinolone hexacetonide on the eighth day of gestation. The frequency of cleft lip in treated *A/J* mice was found to be more than three times greater than the spontaneous frequency in untreated controls. Comparable studies with other murine strains suggest no association between the cleft lip response and either a maternal effect or the H-2 complex. Affected *A/J* embryos showed a severe reduction in the size of the lateral nasal processes; affected embryos also demonstrated localized cell type-specific alterations, particularly in the epithelia and at the interface between epithelium and mesenchyme. Author.

22 MEZZ

AU McCleave-D, Goldstein-J, Silver-S

TI Corticosteroid injections of the nasal turbinates: past experience and precautions

SO Otolaryngology 1978 Nov-Dec, VOL: 86 (6 Pt 1), P: ORL-851-7, ISSN: 0161-6439

AB Clinical experience with triamcinolone acetonide (Kenalog) injections into the nasal turbinates for allergic and vasomotor rhinitis is reported by two authors. Gratifying results have occurred in most of the over 60,000 patients treated, with no serious side effects. Two cases of intravascular injections of another corticosteroid reaching the retinal circulation are reported, and methods for preventing this complication are proposed. Author.

23 MEZZ

AU Silverman-S, Merten-D-F, Anderson-J-H, Hendrick-A-G

TI Radiographic diagnosis of choanal atresia induced prenatally with triamcinolone in the baboon (*Papio cynocephalus*)

SO J-Med-Primatol 1977, VOL: 6 (5), P: 284-97, ISSN: 0047-2565

AB Choanal atresia was diagnosed radiographically using a water soluble contrast media in 2 of 7 *Papio cynocephalus* exposed to triamcinolone acetonide in utero. In one *P. cynocephalus*, the atresia was complete and was associated with other cranial abnormalities. The other animal, previously considered to be normal, had a partial nasal obstruction. The radiographic appearance of the drug-induced defects observed in the baboon closely resemble the descriptions of spontaneously occurring defects in human infants. Author.

24 MEZZ

AU Baker-D-C.

TI Treatment of obstructing inferior turbinates with intranasal corticosteroids.

SO Ann-Plast-Surg 1979 Sep, VOL: 3 (3), P: 253-9, ISSN: 0148-7043.

AB The most common cause of nasal obstruction is chronic enlargement of the inferior turbinate bones. The variety of medical and surgical treatments available for this condition bears testimony to their frequent ineffectiveness and the frustration of the physician or surgeon caring for these patients. Removal or destruction of the inferior turbinates has received strong criticism from rhinologists, although at present there is renewed interest in turbinectomy combined with rhinoplasty. A technique employing intranasal injections of long-acting corticosteroids has been used successfully for over twenty years in treating obstructing inferior turbinates secondary to allergic and vasomotor rhinitis. The indications, technique, and complications of this method are reviewed; the technique is presented as an alternative to destruction or resection of the inferior turbinates. Author.

25 MEZZ

AU Mabry-R-L.

TI Intratubinal steroid injection: indications, results, and complications.

SO South-Med-J 1978 Jul, VOL: 71 (7), P: 789-91, 794, ISSN: 0038-4348.

AB Intratubinal injection of steroid can yield rapid relief of nasal obstruction caused by severe allergic or vasomotor rhinitis, rhinitis medicamentosa, or acutely enlarged nasal polyps. This modality is not meant to replace the traditional means of therapy for these diseases. Despite previous reports of visual loss after intratubinal steroid, thousands of such injections have been given with no such disastrous complications. The technic should include preliminary topical cocaineization of the nasal mucosa, slow injection using a small gauge needle, and steps to allay apprehension and prevent a "needle reaction." In a retrospective study comparing intratubinal triamcinolone with intramuscular betamethasone, the intratubinal steroid was judged much more effective. Side effects reported after intranasal steroid were minor in nature. No visual complications have occurred in this series. Author.

26 MEZZ

AU Sierstad, I Amsaleg-A.

TI (Quick and easy treatment for allergic polyps of the nasal fossae (proceedings))

SO Ann-Otolaryngol-Chir-Cervicofac 1977 Jan-Feb, VOL: 94 (1-2), P: 34, ISSN: 0003-438X.

27 MEZZ

AU Gordon-W-W, Cohn A-M, Greenberg-S-D, Komorn-R-M.

TI Nasal sarcoidosis.

SO Arch-Otolaryngol 1978 Jan, VOL: 102 (1), P: 11-4, ISSN: 0003-9977.

AB Nasal sarcoidosis may affect nasal skin, mucosa, or bone separately or simultaneously. Its incidence in patients with systemic sarcoid was once thought to be low, but this may be due to lack of proper intranasal examination and awareness of its existence by physicians who are more preoccupied with lung and other visceral involvement. The otolaryngologist should be aware of nasal sarcoidosis because nasal obstruction or drainage secondary to nasal sarcoidosis may be the first and only manifestation of systemic sarcoidosis. The otolaryngologist can diagnose this disease earlier in its course by being aware of its existence. Author.

28 MEZZ

AU Myers-D, Myers-E-N

TI The medical and surgical treatment of nasal polyps

SO Laryngoscope 1974 May, VOL: 84 (5), P: 833-47, ISSN: 0023-852X

29 MEZZ

AU Furkert-K

TI (Rhinologic agents 14)

SO Pharm-Prax 1967, VOL: 9, P: 255-8, ISSN: 0048-3656 96 Refs

30 MEZZ

AU Rowe-A-H, Rowe-A-Jr

TI Perennial nasal allergy due to food sensitization

SO J-Asthma-Res 1965 Dec, VOL: 3 (2), P: 141-54, ISSN: 0021-9134

END OF DOCUMENTS IN LIST

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20120/000	Priority: 3S	Org Code: 570
Stamp: 28-APR-1992 Regulatory Due:	Action Goal:	District Goal: 17-JUN-1996
Applicant: MURO PHARM	Brand Name: TRINASAL NASAL SOLUTION	
890 EAST ST	Established Name:	
TEWKSBURY, MA 01876	Generic Name: TRIAMCINOLONE ACETONIDE	
	Dosage Form: SPR (SPRAY)	
	Strength: 0.05%	
<hr/>		
FDA Contacts: S. BARNES (HFD-570)	301-827-1050	, Project Manager
B. ROGERS (HFD-570)	301-827-1065	, Review Chemist
G. POOCHIKIAN (HFD-570)	301-827-1050	, Team Leader

Overall Recommendation:

ACCEPTABLE on 01-FEB-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

ACCEPTABLE on 28-AUG-1997 by M. EGAS (HFD-322) 301-594-0095

ACCEPTABLE on 11-OCT-1996 by M. EGAS (HFD-322) 301-594-0095

Establishment: []

DMF No: []

AADA No: []

Profile: CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 01-FEB-2000
 Decision: WITHHOLD
 Reason: FACILITY (FIRM) WITHDRAWN

Responsibilities: []

Establishment: 1219387
 MURO PHARMACEUTICAL INC
 890 EAST ST
 TEWKSBURY, MA 018761496

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 01-FEB-2000
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION
 Profile: LIQ OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 01-FEB-2000
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE RELEASE
 TESTER
 FINISHED DOSAGE
 MANUFACTURER

Establishment: []

DMF No: []

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

[]

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-SEP-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: []

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CDER Establishment Evaluation Report
for July 17, 1997

Page 1 of 1

Application: NDA 20120/000
Stamp: 28-APR-1992 Regulatory Due:
Applicant: MURO PHARM
890 EAST ST
TEWKSBURY, MA 01876

Priority: 3S
Action Goal:
Brand Name: TRINASAL NASAL SOLUTION
Established Name:
Generic Name: TRIAMCINOLONE ACETONIDE
Dosage Form: SPR (SPRAY)
Strength: 0.05%

Org Code: 570

District Goal: 17-JUN-1996

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 11-OCT-1996 by M. EGAS (HFD-322) 301-594-0095

Establishment: 1219387
MURO PHARMACEUTICAL INC
890 EAST ST
TEWKSBURY, MA 018761496

DMF No:

AADA No:

Profile: LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDAT 18-JUN-1996

Responsibilities:
DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER

Profile: NEC OAI Status: NONE
Last Milestone: OC RECOMMENDAT 10-OCT-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: { }

DMF No: _____

AADA No:

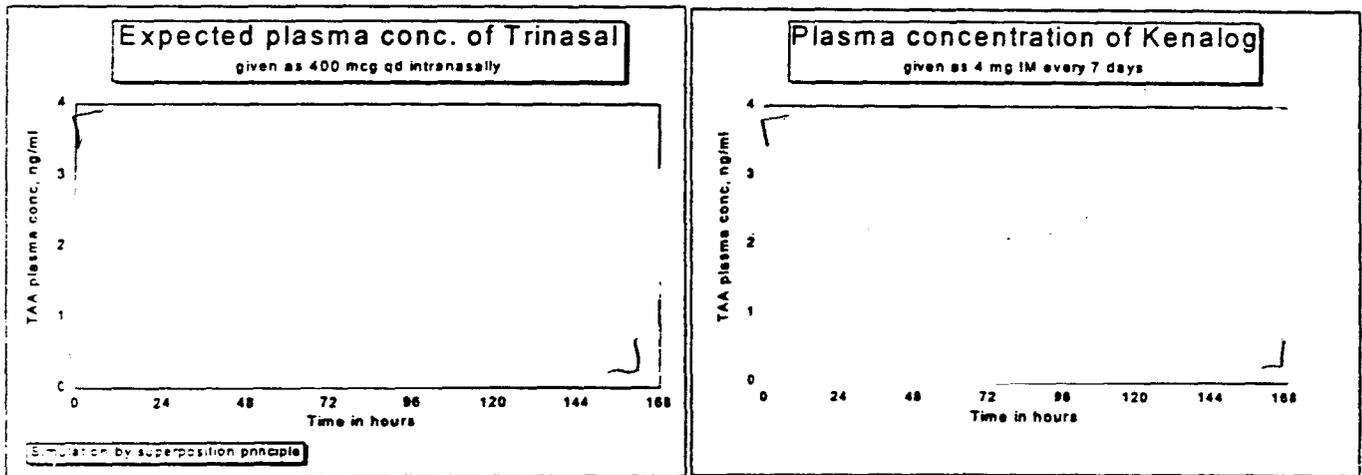
Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDAT 11-MAR-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

APPEARS THIS WAY
ON ORIGINAL

individual nasal symptoms throughout the trial whereas the 50ug dose only showed efficacy at week 3 or weeks 2-3 (for rhinorrhea and itchy nose/throat, respectively). Depending on the individual symptom, the intramuscular formulation showed efficacy at weeks 2-4.

The following two graph (created by Dr. Uppoor) depict the pharmacokinetics of Tri-nasal (simulated based on single dose pharmacokinetics) and Kenalog, the intramuscular formulation:



As can be seen, the exposure to triamcinolone when given as Tri-nasal on a daily basis is higher than the exposure to triamcinolone from a weekly intramuscular injection of Kenalog. Therefore, while this study does support the efficacy of the 400ug per day dose, it does not support the topical effect of Tri-nasal. The Kenalog formulation did demonstrate some limited efficacy and the greater efficacy for the 400ug dose of Tri-nasal could be based on greater systemic exposure, not a topical effect.

Study 0501 is a 4 week double blind, randomized, placebo controlled trial of 200ug of Tri-nasal administered twice daily to patients with SAR. In this trial subjects treated with Tri-nasal experienced statistically significant improvement in sneezing, nasal congestion, nasal secretions and itchy nose/throat/palate compared to placebo for all 4 weeks of the trial. A symptom complex was not calculated for this trial.

The final adequate and well controlled efficacy trial is study 100-305. In this study patients with SAR were randomized to receive either 50, 200 or 400ug per day of Tri-nasal (administered once daily) or placebo for 4 weeks. As with the 50ug dose used in study 100-204, the pump used in this trial delivered — ug per actuation. In addition, the 200ug dose was administered using a pump that delivered — ug per actuation. In this trial, subjects receiving the 50 and 200ug per day

August 21, 1996

regimens experienced statistically significant improvements in the symptom complex, sneezing and nasal congestion for the duration of the trial. Statistical differences from placebo for rhinorrhea were only seen at week one. No statistically significant differences were seen between the 400ug treatment arm and placebo group. While it is unclear why the 400ug treatment arm failed in this trial, the study does support the efficacy of the two lower doses. This study should be considered adequate to support the efficacy of these two doses despite the difference in concentration of triamcinolone used in this trial vs the to be marketed formulation (the 50 and 200ug doses used a _____ concentration whereas the marketed product will deliver 50ug/100ul), since there is no reason to presume that a more concentrated formulation should be less efficacious.

Two additional placebo controlled trials were conducted, one in patients with perennial allergic rhinitis (PAR) and one in patients with SAR. The study in patients with PAR evaluated 200ug of Tri-nasal administered once daily vs placebo in a total of 30 patients for 6 weeks. No statistically significant differences between drug and placebo were seen on the primary endpoints of runny nose and nasal congestions. The second trial, study 4-0501, evaluated 100 or 200ug administered once daily vs placebo to a total of 80 patients with SAR for 4 weeks. No significant differences from placebo were seen.

In summary, efficacy for the 200ug and 400ug doses has been demonstrated and one trial also supports the efficacy of 50ug per day. Additional clinical efficacy issues include the following:

1. **Change in valve:** As noted in the medical officer review, the to-be-marketed drug will include a different valve as compared to the drug used in the clinical trials. Since this is a nasal spray solution, this issue can be addressed with chemistry in vitro data.
2. **Efficacy in the pediatric population (age 12-16 years):** all the clinical trials described above were conducted in subjects age 18 years or greater. While this should not preclude approval of Tri-nasal for use in that age population, particularly since there is some safety data available from that age group and there is no basis to presume that either efficacy or the pharmacokinetics of the drug will be different in subjects age 12-16 years as compared to subjects greater than 16 years, _____
3. **PAR:** There are no data in this NDA which demonstrate the efficacy of Tri-nasal in patients with PAR. As noted in the Division's Points to Consider document for nasal sprays, if a sponsor already has a drug approved for both SAR and PAR and then reformulates that drug, they need not study the drug for both indications. Whether this can be applied to Tri-nasal depends on resolution of the 505(b)(2) issue, specifically whether a bio-inequivalent reference is acceptable and if 505(b)(2) applications can rely on efficacy data from the reference product or just pre-clinical data.
4. **End of Dosing Interval:** As noted above, none of the clinical trials specifically evaluated efficacy at the end of the dosing interval. While it would have been optimal to do so, lack of demonstration of efficacy at the end of the dosing interval should not

preclude approval of this drug, particularly if the application is considered an acceptable 505(b)(2) application, since a steroid would presumably have more of a disease modifying effect rather than acute onset and offset of effect and Nasacort is currently approved for once daily administration.

5. 505(b)(2): As noted above, a number of issues depend on determining whether this is an acceptable 505(b)(2) application.

Safety:

See the medical officer review for a description of the hypothalamic-pituitary-adrenal (HPA) axis cosyntropin stimulation study. The following table depicts the sponsor's analysis of the AUC and peak cortisol level changes from day 1 to day 43. This analysis included the 0 hour values of the respective days:

Treatment	Change in AUC	Change in Peak Cortisol
Placebo	-8.1	2.9
Prednisone	-109.7	-15.0
Tri-nasal 400	-20.4	0.2
Tri-Nasal 800	-25.1	-0.8
Tri Nasal 1600	-32.7	-4.5

Based on discussion with Dr. Guo, the Biometrics reviewer assigned to this NDA, the prednisone treatment arm was statistically significantly different from placebo, whereas the other treatments were not. However, since the purpose of a cosyntropin challenge is to evaluate the adrenal gland's response to a challenge, a more appropriate analysis would be to exclude the 0 hour time point from the AUC and peak values. Thus AUC should demonstrate the response compared to cortisol levels that day and peak values should demonstrate peak response. Performing such an analysis would be expected to change the results from those depicted in the table above because, as seen in the following table, the mean 0 hour values differ on day 43 compared to day 1.

Treatment	Day 1 Zero Hour Mean	Day 43 Zero Hour Mean
Placebo	20.1	18.25
Prednisone	18.82	10.94
Tri-nasal 400	23.8	20.52
Tri-Nasal 800	22.14	22.4
Tri Nasal 1600	17.86	21.32

Based on these values, one would expect that if the 0 hour values are now excluded from the AUC, the change between day 43 and day 1 should become less negative for placebo, prednisone

and the 400ug dose since part of the decrease in AUC for those treatment arms could be due to a decrease in 0 hour value. For the 1600ug arm, one would expect the change between day 43 and day 1 for AUC to be more negative (a greater difference) since inclusion of the 0 hour values may have blunted calculation of a decreased response to cosyntropin. When Dr. Guo performed the analysis by looking at change on day 43 minus day 1 for AUC above hour 0 and for maximal change in cortisol value from the 0 hour, the following was seen:

Treatment	Change in AUC	Change in Peak Cortisol
Placebo	5.73	3.46
Prednisone	-46.69	-7.16
Tri-nasal 400	5.87	3.52
Tri-Nasal 800	-17.44	-0.74
Tri Nasal 1600	-60.39	-7.94

In this analysis none of the treatment arms were statistically significantly different from placebo. While the positive control in this analysis failed to demonstrate a statistical effect, a numerical effect greater than the other treatment arms was seen. In addition, the Tri-nasal treatment arms at higher than 400ug per day also demonstrated numerical effects on suppression of the HPA response and these findings occurred in a dose related manner. While this trial is quite small (only five patients per treatment arm), there is additional data in the literature which supports the safety of Tri-nasal at the planned clinical doses. Howland III et. al. (J Allergy and Clinical Immunology 1996;98:32-8) evaluated the effects of Nasacort Aq on the HPA axis in 64 patients who received either 220ug or 440ug per day of Nasacort Aq, 10mg per day of prednisone or placebo and had cosyntropin challenge at baseline and week 6. In this trial prednisone was statistically different from placebo whereas the Nasacort Aq treatment arms were not. The C_{max} and AUC for a 440ug dose of Nasacort Aq are .817 ng/ml and 4.678 ng x hr/ml, respectively and for a 400ug dose of Tri-nasal they are 1.27 ng/ml and 3.83 ng x hr/ml, respectively. Of note, in the package insert the sponsor claims

[. This wording will have to be modified to reflect the small size of the trial and to remove the reference to _____]

_____ . Finally, when individual patient data was examined to determine if any patients experienced a blunted response to cosyntropin challenge at day 43 (defined as a response of < 7 and a peak level of < 20) only one patient in the 1600ug arm exhibited such a response.

Regarding the safety of the drug in subjects age 12-16 years, 21 subjects in that age group received 400ug per day of Tri-nasal. Adverse events in this group were similar in type to that seen in subjects older than 16 years.

Overall there were no adverse events or laboratory results that would preclude approval of this drug and there is adequate HPA data as well to support approval of Tri-nasal.

Labeling:

Since this NDA will not be approved due to chemistry issues, detailed labeling comments need not be conveyed at this time. However, the following labeling issues can be sent to the sponsor in the action letter (specific wording can be worked out with the medical officer):

1. Based on re-analysis of the HPA safety study, that study only supports the safety of the 400ug per day dose, _____ addition, there was no statistical effect of prednisone and the small size of the trial should be reflected in the package insert.
2. Based on analysis of the pharmacokinetic data of Kenalog and Tri-nasal, _____

Therefore, this claim should be removed from the package insert.

3. Since the _____ per day dose was not studied in an adequate clinical trial, in the Dosage and Administration section wording that states that "_____ dose should be titrated to the lowest effective dose" should replace the specific instructions for use of a _____ per day dose.

4. As noted in the medical officer review, the adverse event table in the package insert should be based on all placebo controlled trials and should indicate that the control used was vehicle placebo. In addition, to determine the most appropriate format for this table, the sponsor should be asked to submit an adverse event table for our review that contains all adverse events (not just those attributed to the drug) from all placebo controlled trials with the adverse events presented for the 200 and 400ug per day doses separately as well as combined and for placebo.

5. Additional specific labeling comments need not be forwarded to the sponsor at this time, however the action letter should indicate that there will be additional comments in the future.

Overall conclusions:

As indicated above, the safety and efficacy of the 200 and 400ug per day doses of Tri-nasal have been demonstrated in patients with SAR. _____

_____ and chemistry formulation issues will need to be included in the action letter. From the clinical perspective this application is approvable.

cc:

NDA#20-120
HFD-570 Division File
HFD-570/Himmel
HFD-570/Saavedra-Delgado
HFD-570/Steve Wilson

NDA# 20120
Page 7
August 21, 1996

HFD-570/Guo
HFD-570/Conner
HFD-570/Uppoor
HFD-570/Sheevers
HFD-570/Whitehurst
HFD-570/Poochikian
HFD-570/Ng
HFD-570/Barnes

**APPEARS THIS WAY
ON ORIGINAL**