CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-120

CORRESPONDENCE

Printed by Sandra Barnes

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 26-Feb-1998 10:21am
From: Bradley Gillespie
GILLESPIEB
Dept: HFD-870 PKLN 10B31
Tel No: 301-827-1078 FAX 301-827-1273

TO: Sandra Barnes (BARNES)
TO: Mei-Ling Chen (CHENME)

Subject: Tri-Nasal Label

Mrs. Barnes:

As I stated earlier this morning, most of my comments/complaints were directed towards the Nasacort label. My corrections to the PK section are redlined/overstricken in the attached WP file. Mei-Ling, if you need to discuss this label further, please talk to me or Sandy ASAP.

Thanks,
Brad

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 73 PAGE (S)

Draft

Labeling

Muro

July 1, 1996

John Jenkins, M.D.
CDER, Food and Drug Administration
Division of Pulmonary Drug Products, HFD 570
5600 Fishers Lane, Room 10B-03
Rockville, MD 20857

RE: NDA #20-120 Tri-Nasal™ (triamcinolone acetonide 0.05%) Nasal Solution

Dear Dr. Jenkins:

The original return receipt reply from Rhone-Poulenc Rorer documenting receipt of Muro's patent non-infringement notice concerning Muro's Tri-Nasal NDA did not include the date of delivery (RE: NDA Amendment April 9, 1996). The Tewksbury Post Office has issued Muro a Domestic Return Receipt (PS Form 3811-A) which verifies 4/5/96 as RPR's, signed receipt of delivery for a the non-infringement notice.

A copy of this document is enclosed.

Sincerely,

Joseph A. Celona
Director of Regulatory Affairs

JC/mm
Enclosure

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG
REC'D
JUL 2 1996
HFD-570
EVALUATION AND RESEARCH

Muro Pharmaceutical, Inc.
890 East Street, Tewksbury, Massachusetts. 01876-1496
Phone (508) 851-5981 FAX (508) 851-7346

ORIGINAL

FISH & RICHARDSON P.C.

FISH RICHARDSON & NEAVE
BOSTON
(1916-1969)

FREDERICK P. FISH
(1855-1930)

W.K. RICHARDSON
(1859-1951)

601 THIRTEENTH STREET, N.W.
WASHINGTON, D.C. 20005

TELEPHONE: 202/783-5070
FAX: 202/783-2331

BOSTON
617/542-5070

HOUSTON
713/629-5070

SILICON VALLEY
415/322-5070

TWIN CITIES
612/335-5070

SOUTHERN CALIFORNIA
619/678-5070

NEW YORK
212/765-5070

ORIG AMENDMENT

N (XR)

April 9, 1996

Our File: 07215/002001

John Jenkins, M.D.
CDER, Food and Drug Administration
Division of Pulmonary Drug Products
HFD 570
5600 Fishers Lane, Room 10B-03
Rockville, Maryland 20857

Muro Pharmaceutical, Inc.
Patent Certification Notice
Return Receipt for File
NDA 20-120

Dear Dr. Jenkins:

On behalf of Muro Pharmaceutical, Inc., this is to amend the above-captioned NDA. Enclosed please find the signed domestic return receipt from Muro's Patent Certification Notice delivered to Rhone-Poulenc Rorer, Inc., the owner of Patent No. 4,767,612 and holder of the FDA-approved new drug application, NDA 19-798.

Please contact the undersigned attorney if you have any questions.

Very truly yours,

Terry G. Mahn

TGM/smw
Enclosure
cc: Muro Pharmaceutical, Inc.

58201.W11

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ON ORIGINAL

UNITED STATES POSTAL SERVICE

Official Business

PENALTY FOR PRIVATE USE TO AVOID PAYMENT OF POSTAGE, $300

Print your name, address and ZIP Code here

Terry G. Mahn
Fish & Richardson P.C.
601 13th Street, N.W.
Fifth Floor North
Washington, D.C. 20005

24

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Is your RETURN ADDRESS completed on the reverse side?

SENDER:

- Complete items 1 and/or 2 for additional services.
- Complete items 3, and 4a & b.
- Print your name and address on the reverse of this form so that we can return this card to you.
- Attach this form to the front of the mailpiece, or on the back if space does not permit.
- Write "Return Receipt Requested" on the mailpiece below the article number.
- The Return Receipt will show to whom the article was delivered and the date delivered.

I also wish to receive the following services (for an extra fee):

1. ☐ Addressee's Address
2. ☐ Restricted Delivery

Consult postmaster for fee.

3. Article Addressed to:

Mr. Martin F. Sawitzky
Rhone-Poulenc Rorer, Inc.
500 Arcola Road
Collegeville, PA 19426-0107

4a. Article Number

Z 010 101 529

4b. Service Type

☐ Registered ☐ Insured
☒ Certified ☐ COD
☐ Express Mail ☒ Return Receipt for Merchandise

7. Date of Delivery

5. Signature (Addressee)

8. Addressee's Address (Only if requested and fee is paid)

6. Signature (Agent)

PS Form 3811, December 1991 ☆U.S. GPO: 1993—352-714 **DOMESTIC RETURN RECEIPT**

Thank you for using Return Receipt Service.

APPEARS THIS WAY ON ORIGINAL

MIDDLESEX-CENTRAL CUSTOMER SERVICE & SALES DISTRICT

UNITED STATES POSTAL SERVICE

Date: June 19, 1996

To: Mr. Brant T. Sayre
Muro Pharmaceutical, Inc.
890 East St.
Tewksbury, MA 01876

Dear Mr. Sayre,

Here is a PS 3811-A, Domestic Return Receipt After Mailing). Please let me know if this does not provide the information you are looking for.

I am sorry the original form was not correct and apologize for our error.

Please contact me anytime you have a question concerning service.

Thank you,

Linda L. Coan

Linda L. Coan
Officer-In-Charge
Tewksbury Post Office

MAILING OFFICE: Postmark to indicate fee was previously paid for service described in item 2.

TEWKSBURY MA 01876 JUN 10 1996 USPS

Attach applicable fee as shown in DMM for Return Receipt after mailing.

CUSTOMER: Complete unshaded (top) area and enter your name and address on the reverse.

Check box next to desired service:

☒ 1. RECEIPT AFTER MAILING - Provide name of individual, company, or organization to whom delivered and date of delivery

☐ 2a. DUPLICATE RECEIPT - Provide name of individual, company, or organizaton to whom delivered and date of delivery.

☐ 2b. DUPLICATE RECEIPT *(with address of delivery)* - Provide name of individual, company, or organizaton to whom delivered, date of delivery, and addressee's

3. Mailing Date	4. COD Number	5. Return Receipt for Merchandise No.

6. Registered Number	7. Certified Number	8. Insured Number	9. Express Mail Number
	Z010 101 529		

10. Article Addressed To
MR MARTIN F SAUITZKY

11. Delivery Office Postmark		15. ☐ Postal Records Show Delivery Was Made
	12. Delivery Date: 14-5-96	
	14. Address *(Complete only if required)*	16. Clerk's Initials

PS Form **3811-A**, July 1993 Domestic Return Receipt *(After Mailing)*

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-120

SEP 17 1996

Muro Pharmaceutical, Inc.
890 East Street
Tewksbury, Massachusetts 01876-1496

Attention: Joseph A. Celona
Director of Regulatory Affairs

Dear Mr. Celona:

Please refer to your April 27, 1992 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tri-Nasal Spray (triamcinolone acetonide nasal solution, 0.05%).

We acknowledge receipt of your amendments dated October 31, 1995, February 12 and 15, March 7, April 1, 9, 11, 24, and 29, May 7, June 4, July 1, 22, and 24, and August 2, 1996.

We have completed our review of your application, as amended, and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows.

WITHHOLD 9 PAGE (S)

22. Please submit a revised Environmental Assessment (EA) including a releasable copy of the EA in accordance with the following comments.

    a. The names, job title and qualifications of the preparers of the document should be included.

    b. The total certification statement should be included before the signature in the EA.

    c. Tri-Nasal Spray qualifies for a tier 0 environmental assessment [the MEEC for the test article is less than 1part/billion (1 ppb)], therefore items 7, 8, 9, 10, 11, and 15 appendices G, H, I, K, and L should be excluded.

    If you have any questions, please refer to the *Guidance for Industry: For the Submission of an Environmental Assessment in Human Drug Applications and Supplements*, November 1995.

23. The following preliminary comments pertain to the package insert. A revised draft package insert should be submitted which incorporates these comments.

    a. The Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section should include information regarding:

        i. The absence of gender effect on pharmacokinetics of TAA from Tri-Nasal; and

ii. a paragraph describing dose proportionality of intranasal TAA. Suggested wording for the paragraph is as follows.

> A pharmacokinetic study to demonstrate dose proportionality was conducted in perennial allergic rhinitis patients. The C_{max} and AUC of the 200 and 400 ug doses increased less than proportionally when compared to the 100 ug dose.

b. Study 100-204 was not adequately designed to support a topical effect claim for Tri-Nasal; exposure to triamcinolone when given as Tri-Nasal on a daily basis is greater than when administered as a weekly intramuscular injection of Kenalog. Therefore this claim should be removed from the package insert.

c. The sentence

[ ]

found in the first paragraph of the Pharmacodynamics subsection of the CLINICAL PHARMACOLOGY section should either be removed or should state that

[ ]

d. Since the — mcg per day dose was not studied in an adequate clinical trial, wording that conveys that as with any corticosteroid, once relief is obtained the daily dose should be

titrated to the lowest effective dose, should replace the specific instructions for use of a — mcg dose in the DOSAGE AND ADMINISTRATION section.

e. The description of study 1-0501 found in the third paragraph of the Pharmacodynamics subsection of the CLINICAL PHARMACOLOGY section should be modified to reflect the small size of the trial and to remove the reference to the

as well as the claim that there was a This is based on re-analysis of this study looking at response to cosyntropin challenge: a numerical dose effect of suppression by Tri-Nasal is seen and the prednisone effect is no longer statistically significantly different from placebo.

f. 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. Please 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 400 mcg per day doses separately as well as combined, in order to determine the most appropriate format for this table in the package insert.

g. Please refer to the attached draft approved Nasacort Nasal Inhaler package insert for guidance in updating the preclinical section of the proposed Tri-Nasal package insert.

We may have additional labeling comments following our review of the requested CMC data and the requested draft labeling incorporating the above comments.

In addition, we advise you to contact this Division prior to submission of a supplemental application, _____ in order to determine the extent of data needed to support this type of supplemental application.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact:

Sandy Barnes
Project Manager
(301) 827-1075

Sincerely yours,

/S/

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Rec 8/17/92

AUG 14 1992

NDA 20-120

Muro Pharmaceutical Incorporated
890 East Street
Tewksbury, Massachusetts 01876

Attention: Joseph A. Celona
Director, Regulatory Affairs

Dear Mr. Celona:

Please refer to your new drug application dated January 17, 1992 submitted pursuant to section 505(a) of the Federal Food, Drug, and Cosmetic Act for Trinasal (triamcinolone acetonide nasal solution 0.05%).

We also note our telephone conversation on August 4, 1992.

We have completed our review and find the information presented is inadequate and the application is not approvable. The major and minor deficiencies are summarized as follows.

CLINICAL:

MAJOR:

1. The lack of long term safety data on Trinasal patients. (At least 300 patients with safety data up to 6 months will be needed).

2. The lack of an acceptable clinical topical effect study at the appropriate oral dose. (The design and dosing selection of this study should be discussed with the division).

3. Inadequate efficacy analysis; i.e, lack of an appropriate placebo symptomatic day analysis.

4. Lack of a therapeutic dose response study.

PHARMACOKINETICS:

MAJOR:

1. The lack of an adequate and established assessment of the systemic absorption and dose proportionality profile that is required for approval of an NDA under the regulations for any drug product.

2. The lack of an *in vivo* assessment of the pharmacokinetics of Trinasal (triamcinolone acetonide nasal solution 0.05%) following single an multiple doses.

CLINICAL/PHARMACOKINETIC:

MAJOR:

1. Lack of a therapeutic and pharmacokinetic comparison to the currently marketed innovator.

PHARMACOLOGY:

MAJOR:

1. The lack of carcinogenicity studies.

CHEMISTRY:

MAJOR:

1. The limits on the Quantity Delivered per Spray specification are too wide. The usual limits are ——— for the average and ——— individual ———

MINOR:

1. Please explain why the solution is formulated with ———

2. [ ]

3. The typo in the specification should be corrected - should read

4. Please provide the following information on the bottles made by

Items may be referenced to a DMF via a letter of authorization from the DMF holder.

The above chemistry deficiencies were faxed to you on August 7, 1992.

ALL REVIEW AREAS:

The format of the submission does not allow ready access to the data/information that is contained in the NDA nor does it facilitate any additional reviewer performed data manipulation. In addition the chemistry portion is not formatted in accordance with the guidelines. The specifics of these issues should be discussed with the review team.

CONCLUSIONS:

If you are interested in refiling this NDA, we will be glad to discuss the deficiencies and to also identify what we feel you need to do in order to file an NDA and produce one that is potentially reviewable in 180 days.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may withdraw the application. A partial response will not be processed as a major amendment, and, therefore, the review clock will not be activated.

Should you have any questions, please contact:

Frances V. LeSane
Project Manager
(301) 443-3741

Sincerely yours,

The Review Team of the Pilot Drug Evaluation Staff, Center for Drug Evaluation and Research:

/S/
John G. Harter, M.D.
Director, PDES

/S/
E. Dennis Bashaw, Pharm.D.
Pharmacokineticist

/S/
Patricia Y. Love, M.D.
Medical Officer

/S/
Conrad Chen, Ph.D.
Pharmacologist

/S/
Charlotte A. Yaciw
Chemist

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 5, 1999

FROM: Sandy Barnes
Project Manager

SUBJECT: NDA 20-120 Labeling and Nomenclature Consultation

TO: The File

An April 4, 1996 consultation from the CDER Labeling and Nomenclature Committee recommended against the use of Tri-Nasal as a proposed trademark for this product. The committee objected to "tri" as it could imply the number of doses or number of times per day the product should be used. In addition, the committee was concerned that the "tri" could be used for promotional purposes, as in "try". The committee also objected to the use of the route of administration in the trademark. They did recognize that there is precedent for the use of both "tri" and "nasal", however they found the trademark unacceptable.

In consultation with the Division and Office Directors at the time of the consult, the team made the decision to allow the use of the trademark.

Consult #543 (HFD-570)

TRI-NASAL SPRAY triamcinolone acetonide nasal solution 0.05%

The Committee was concerned that Tri- in the trademark implies three and could be confused with the number of doses or the number of times per day that the medication should be used. Additionally, there is a promotional aspect that "tri" will be used as "try" in marketing campaigns. In general, the route of administration should also be avoided in a trademark since alternate dosage forms may be developed which utilize a different route of administration. The Committee is aware that many precedent names have used both "Tri" and "Nasal" in the trademarks, however the Committee recommends against the use of this proposed trademark based on the preceding objections.

The Committee finds the proposed trademark to be unacceptable.

/S/ 4/4/96, Chair

CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL