CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40378

CORRESPONDENCE

ANDA 40-378

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins
14905 23rd Avenue North
Minneapolis, MN 55447

AUG 17 1999

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated August 11, 1999 and your correspondence dated August 12, 1999.

NAME OF DRUG: Niacin Tablets, USP, 500 mg

DATE OF APPLICATION: July 19, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 20, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dilahunt
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

April 11, 2000

FEDERAL EXPRESS

ORIG AMENDMENT
MIAM

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 40-378; Niacor® (Niacin Tablets, USP) 500 mg
MINOR AMENDMENT Responding to the Agency's March 17, 2000 Deficiency Letter

CHEMISTRY INFORMATION INCLUDED

Dear Mr. Buehler:

Reference is made to the Upsher-Smith Laboratories, Inc. pending ANDA 40-378 for the above referenced drug product.

Reference is also made to the Agency's March 17, 2000 deficiency letter.

In response to the deficiency letter, this amendment is submitted herewith to the above referenced ANDA. This amendment has been designated as a MINOR AMENDMENT. Each deficiency item is shown in bold print and has been addressed in the sequence presented in the deficiency letter.

A. Deficiencies:

DMF remains deficient. Please confirm a response to our recent letter before amending this ANDA.

Upsher-Smith has contacted holder of DMF and confirms that a response to the DMF deficiency has been provided to the Agency. Upsher-Smith also confirmed, via telephone communication with Michelle Dillahunt, Project Manager, that the Central Document Room has received the DMF update and deficiency response.

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 763-473-4412 FAX #763-476-4026 Sales & Distribution 1-800-654-2299

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comment in your response:

A satisfactory compliance evaluation is necessary for approval. We are awaiting the report from the Office of Compliance.

Upsher-Smith acknowledges that a satisfactory CGMP evaluation is required before the application can be approved. Minneapolis District FDA conducted a pre-approval inspection at Upsher-Smith for ANDA 40-378 on November 15-17 and 19, 1999, resulting in an acceptable compliance status from the Minneapolis District FDA. A copy of the January 5, 2000 District FDA Post-Inspection Notification and Establishment Inspection Report is attached for your reference. Upsher-Smith contacted the Minneapolis District FDA and confirmed that an approvable status was forwarded to the Office of Compliance on December 16, 1999.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

As required per 21 CFR 314.96(b), we hereby certify that a field copy of this amendment, dated April 10, 2000, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

If there are any questions or comments regarding this amendment, please contact Michael Poirier, Regulatory Affairs Specialist, at (763) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D., J.D.
Vice President, Scientific Affairs

MSR/bac

Enclosures

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

March 3, 2000

NDA ORIG AMENDMENT

N/A 1

FEDERAL EXPRESS

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 40-378; Niacor® (Niacin Tablets, USP) 500 mg
MINOR AMENDMENT Responding to the Agency's January 31, 2000 Deficiency Letter

CHEMISTRY AND LABELING INFORMATION INCLUDED

Dear Mr. Buehler,

Reference is made to Upsher-Smith Laboratories, Inc. pending ANDA 40-378 for the above referenced drug product.

Reference is also made to the Agency's January 31, 2000 deficiency letter.

In response to the deficiency letter, this amendment is submitted herewith to the above referenced ANDA. This amendment has been designated as a MINOR AMENDMENT. Each deficiency item is shown in bold print and has been addressed in the sequence presented in the deficiency letter.

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX= 612-476-4026 Sales & Distribution 1-800-654-2299

I. CHEMISTRY

A. Deficiencies

1. **The DMF for the drug substance, Niacin USP is found deficient and the DMF holder has been informed. Please confirm a response.**

   Upsher-Smith has contacted , holder of DMF , and confirms that a response to the DMF deficiency, dated February 21, 2000, has been provided to the Agency. A copy of the response is provided in Attachment 1 for the reviewer's convenience.

2. **Please clarify if you will use any of the proposed contract laboratories to test drug substance or drug product (chemical or microbial tests).**

   Upsher-Smith will perform all drug substance and drug product testing. Contract laboratories proposed in the original submission will not perform drug substance or drug product testing, but may conduct inactive ingredient raw material testing as appropriate.

3. **Your sample preparation procedure for IR (ID test) for the drug product, Niacin Tablets USP is different from the compendial test method. Please demonstrate that there would be no matrix interference in the IR "fingerprint" region, which may be caused by those excipients used in your formulation.**

   Using the test method provided in the original application, a sample of the Niacor matrix (i.e., excipients in the same proportion as the finished drug product) was prepared, analyzed and compared against the similarly prepared original Niacor® (Niacin Tablets, USP) Exhibit Batch, manufacturing Lot 64892, IR scan. The corresponding IR scans are provided in Attachment 2 with a Niacin Reference Standard IR scan for the reviewer's convenience. Although the matrix had an additive effect on the two maxima having the largest absorbance, the contribution of the matrix does not provide any significant differences in the pattern of the niacin fingerprint region. Upsher-Smith, however, has decided to adopt the USP procedure. The current test method for Identification Test A (IR) has been changed to the USP methodology. The proposed test method, Niacor® Tablet Identification Using Infrared and Ultraviolet Spectrophotometry combines Identification Test A (IR) and Identification Test B (UV) and is provided in Attachment 3.

The Niacor® Exhibit Batch was retested to show conformance to the USP Identification Test A for Niacin Tablets. An executed Analytical Results Form with the corresponding scans are provided in Attachment 4. Test method Niacor® Tablet Identification Using Infrared and Ultraviolet Spectrophotometry, will be performed on all production lots of Niacor® Tablets.

Since the method numbers for Identification Test A (IR) and Identification Test B (UV) were changed, the Analytical Results Form has been revised to include the new method, In addition, for clarification purposes, a retention time difference (NMT minutes) was added to the Identification Test C specification on the Analytical Results Form. The current method, Chromatographic Identification - Retention Time, includes a calculation of the retention time difference between the sample and standard injections. The Analytical Results Form has been revised to document this retention time difference. No changes have been made to the actual test method.. A copy of the revised Analytical Result Form is provided in Attachment 5.

4. **Please acknowledge that you will provide at least three batches of adequate stability data before you extend your expiration dating period in an Annual Report.**

   Upsher-Smith acknowledges that prior to extending the expiration dating period for Niacor® Tablets, at least three batches of adequate stability data will be generated according to the protocol provided in the original ANDA submission and subsequently submitted to the Agency in an Annual Report as required per 21 CFR 314.70(d)(5).

B. **In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:**

1. **The CGMP status of the firms referenced in the ANDA are currently being evaluated by our Office of Compliance. A satisfactory evaluation is required for approval.**

   Upsher-Smith acknowledges that satisfactory CGMP evaluations are required for the firms referenced in the original submission before the application can be approved.

2. **Your response must also address the labeling deficiencies.**

   Please refer to the responses to comment II. A. and II. B.

3. **Please provide any additional long term stability data that is available.**

   The updated Niacor® (Niacin Tablets, USP) Exhibit Batch controlled room temperature Stability Profile is provided in Attachment 6. The stability data includes testing through 12 months. No stability issues or degradation trends are apparent.

4. **The USP analytical methods, as written, are considered regulatory and shall rule in the event of a dispute.**

   Upsher-Smith acknowledges that USP analytical methods are considered regulatory methods and will be used by the Agency accordingly.

II. LABELING

A. Auxiliary Sticker

1. **Satisfactory in draft. [NOTE: This auxiliary sticker should be used only for the first 6 months the product is marketed.]**

   Upsher-Smith confirms that the auxiliary sticker will only be used for the first six (6) months the product is marketed.

B. Insert

1. **Title**

   We encourage the inclusion of "Rx only" in this section. Relocate "Rx only" from the HOW SUPPLIED SECTION.

   Per CDER's *Guidance for Industry, Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997—Elimination of Certain Labeling Requirements*; Revised, July 1998, amending the FD&C Act, Section 503(b)(4), Upsher-Smith chooses not to relocate the "Rx only", but to delete it from the package insert entirely. The package insert has been revised accordingly.

   Twelve copies of final printed labeling are provided in Attachment 7.

To facilitate review of this amendment, and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the revised, proposed package insert labeling (Rev. 0200) to the labeling submitted in the original application (Rev. 0399), is provided in Attachment 8.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

As required per 21 CFR 314.96(b), we hereby certify that a field copy of this amendment, dated March 3, 2000, has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

Should you have any questions or comments regarding this amendment, please contact Michael Poirier, Regulatory Affairs Specialist, at (763) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

Enclosures

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Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

July 19, 1999

FEDERAL EXPRESS

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Mr. Sporn:

RE: Original Abbreviated New Drug Application (ANDA) for Niacor® (Niacin Tablets, USP) 500 mg

Submitted herewith, please find an original ANDA for Niacor® (Niacin Tablets, USP) 500 mg. This drug is equivalent to the reference drug, Nicolar® (Niacin Tablets, USP), manufactured by Rhone-Poulenc Rorer, ANDA 83-823.

Upsher-Smith Laboratories, Inc. (the ANDA applicant) is located at:

14905 23rd Avenue North
Minneapolis, MN 55447
Telephone: (612) 473-4412
Telefax: (612) 476-4026

This original ANDA is being submitted, in duplicate, as an archival and review copy. The archival copy (blue jackets) consists of 2 volumes. The review copy contains two parts; the chemistry, manufacturing and controls data consisting of 2 volumes (red jackets), and the bioavailability/bioequivalence data consisting of 1 volume (orange jacket).

Because an AA therapeutic equivalence code has been designated for this product, no clinical data are provided. Section VI, *In Vivo* Bioequivalence and *In Vitro* Test Data, consists of a request for waiver of *in vivo* bioequivalence and corresponding *in vitro* test data.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of the chemistry, manufacturing and controls sections of this ANDA has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of the technical sections of this application.

If you have any questions or comments regarding this submission, please contact Cindy Farner, Senior Regulatory Affairs Specialist at (612) 449-7267.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

Enclosures