

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:74-962

CORRESPONDENCE



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

505(S)(2)(a)(ok)
Aure Marie H. White
11/18/96
/S/
11/19/96

September 17, 1996

FEDERAL EXPRESS

RECEIVED

SEP 20 1996

GENERIC DRUGS

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 Pentoxil™ (Pentoxifylline Extended-release Tablets, 400 mg)

Submitted herewith, please find an original ANDA for Pentoxil™ (Pentoxifylline Extended-release Tablets, 400 mg). This drug is the same as the reference drug, Trental® (Pentoxifylline Tablets, 400 mg), Hoechst-Roussel NDA 18-631.

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

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

This original ANDA is being submitted, in duplicate, as an archival and review copy. The archival copy (blue jackets) consists of 14 volumes. The review copy contains two parts; the chemistry, manufacturing and controls data consisting of 4 volumes (red jackets), and the bioavailability/bioequivalence data consisting of 11 volumes (orange jackets).

UPSHER-SMITH

Douglas Sporn
September 17, 1996
Page 2

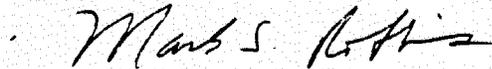
The bioequivalence clinical data are provided on disk in ASCII format. These disks are submitted in the front of Section VI (Volume 2) of this application.

As required per 21 CFR 314.94(d)(5) [p. 139 of the 1995 revision of 21 CFR], 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 as well. This third (field) copy is a "true" copy of the technical sections of the application.

Should you have any questions or comments regarding this submission, please call Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.



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

MSR/bac

c: Food and Drug Administration
Minneapolis District Office
240 Hennepin Avenue
Minneapolis, MN 55401

enclosure

ANDA 74-962

Upsher-Smith Laboratories
Attention: Mark S. Robbins, Ph.D.
14905 23rd Avenue North
Minneapolis, MN 55447-4709

DEC 10 1996

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.

NAME OF DRUG: Pentoxifylline Extended-release Tablets, 400 mg

DATE OF APPLICATION: September 17, 1996

DATE OF RECEIPT: September 20, 1996

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:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours

/s/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

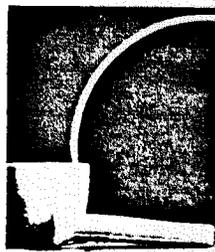
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ANDA 74-962

cc:

Endorsement:

HFD-615/ERICAMM, Chief, RSB Ericamm date 12/9/96
HFD-615/AMWeikel, CSO AMWeikel date 11/20/96
HFD-647/JSimmons, Sup. Chem. _____ date _____
X:\WPFILE\ANNA\74\74962.ACK
F/T
ANDA Acknowledgement Letter!



AMENDMENT
N/A

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

February 12, 1997

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

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: Amendment 001 to ANDA #74-962
Pentoxil™ (Pentoxifylline Extended-release Tablets, 400 mg)
Gratuitous Amendment to Provide Summary Table of Packaging Information**

Reference is made to Upsher-Smith Laboratories, Inc. pending ANDA #74-962 for the above referenced drug product.

Reference is also made to the Agency's letter dated December 1, 1995 (reference number OGD 95-297), which gives the Agency's response and approval of Upsher-Smith's proposed packaging plan for Pentoxil™ lot #61037.

In the Agency's December 1, 1995 letter, it was requested that Upsher-Smith submit as part of the ANDA "a summary table of packaging information describing the container/closure system, the total number of containers packaged and the quantity disbursed, and the destination of all disbursements of the packaged product." During the course of Minneapolis District FDA's Pre-Approval Inspection for this application, Ms. Sharon Thoma, Investigator, noted that a summary

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FEB 19 1997

UPSHER-SMITH

14905 23rd Avenue North - Minneapolis, MN USA 55447
Corporate Headquarters 612-473-4412 FAX: 612-476-4026 Sales & Distribution 612-473-9554-2299

GENERIC DRUGS

Douglas Sporn
February 12, 1997
Page 2

table had not been included with the ANDA. It was explained that the exclusion of an actual summary table was an oversight, however, all information requested in the Agency's letter was included in the executed packaging records, submitted in the In-Process Controls section of the ANDA. This observation, however, was included on the Form FDA 483.

This Amendment provides the summary table of the packaging information requested in the Agency's letter. Pursuant to a phone communication with Mr. Jim Wilson, CSO, Office of Generic Drugs, concerning the proper way to amend the application with this information so as not to restart the review cycle, this Amendment has been labeled as a "Gratuitous Amendment" submitted pursuant to the 483 observation.

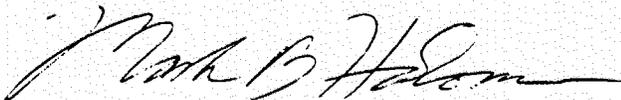
This Amendment 001 is being submitted in duplicate for incorporation into our file.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this Amendment has been submitted to the Minneapolis District Office for their review as well.

Should you have any questions or comments regarding this submission, please call Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Mark B. Halvorsen, Pharm.D.
Manager
Clinical and Regulatory Affairs

MBH/bac

Enclosures 2

Page(s) 4

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

THIS AMENDMENT.

B. Labeling Deficiencies

Upsher-Smith acknowledges that the proposed Pentoxil™ tradename has been sent to the CDER Labeling and Nomenclature Committee for their review and comments.

All labeling deficiencies enumerated in the Agency's letter have been corrected and the labeling revised accordingly.

Labeling comparisons as well as examples of final printed labeling are included herewith as Attachment #8. Twelve sets of final printed labeling are included with the archival copy of this amendment.

In addition to responding to the items enumerated in the Agency's deficiency letter, the following information is provided:

- Updated stability data are provided as Attachment #9.
- The Standard Operating Procedure (SOP) # [redacted] for "Operation, Cleaning and System Verification of the [redacted] Moisture Analyzer", referenced in Steps [redacted] and [redacted] in the Pentoxil™ master batch record has been transferred from the Research and Development department to the Formulations department. This SOP has now been renumbered as SOP# [redacted] and referenced as such in Steps [redacted] and [redacted] the master batch record. No other changes were made to the SOP. Updated pages of the master batch record are provided as Attachment #10.
- The following Raw Material Specification Sheets have been updated as described below. Copies of the updated specification sheets are provided as Attachment #11.
 - ◊ The specifications for testing Purified Water, USP have been updated to comply with the current compendia (USP 23, Supplement 5). That portion of the Raw Material Specification Sheet for Purified Water, USP that covers testing of the [redacted] was revised to replace [redacted] and [redacted] testing with a chloride limit test.
 - ◊ The specifications for testing Hydroxypropyl Methylcellulose [redacted] SP [redacted]) have been updated to comply with the current compendia (USP 23, Supplements 3 and 5).
- The following raw material and finished product test methods have been revised as described below. Copies of the updated methods are provided as Attachment #12.
 - [redacted] general test method for Description, was revised to change the prefix of the method number to QS to conform to the current department name (Quality Services). The new revision, [redacted] includes minor editorial changes for clarification as well.
 - [redacted], Chemical Testing For USP Purified Water, was revised to incorporate testing changes per the current compendia (USP 23, Supplement 5). The new revision, [redacted] also incorporates a chloride test as an additional test used when testing the transfer hoses. Other minor editorial changes were made for clarification.

Mr. Douglas Sporn

April 30, 1997

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“Stability Indicating Assay for Pentoxifylline Tablets and Raw Material”, was revised pursuant to an observation made by Ms. Sharon Thoma, FDA Investigator, during the Pre-approval Inspection for this ANDA. The new revision, requires that all stock working standards of pentoxifylline and well as stock sample preparations are prepared fresh daily. The term “daily” is defined as within 24 hours.

“Pentoxifylline Dissolution”, was also revised pursuant to the above referenced observation made by Ms. Thoma during the Pre-approval Inspection. The new revision, requires that all standard solutions are prepared fresh daily. The method also requires that all samples are analyzed within a 24 hour period of the time they were withdrawn.

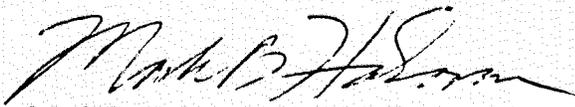
This Amendment #002 is being submitted in duplicate for incorporation into our file.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this Amendment #002 has been submitted to the Minneapolis district FDA for their review as well.

Should you have any questions regarding the information contained herein, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612)449-7261.

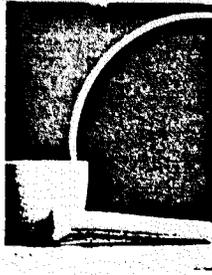
Sincerely,

UPSHER-SMITH LABORATORIES



Mark B. Halvorsen, Pharm. D.
Manager
Clinical and Regulatory Affairs

enclosure



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

^{yes this}
BIOAVAILABILITY

NC/110

September 8, 1997

FEDERAL EXPRESS

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence
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 20855-2773

Dear Dr. Fleischer:

RE: ANDA 74-962

***Pentoxil™ (Pentoxifylline Extended-release Tablets, 400 mg)
Major Amendment #003 to Provide Response to the Agency's July 10, 1997
Deficiency Letter***

Reference is made to our pending Abbreviated New Drug Application #74-962 for the above referenced drug product.

In response to the Agency's deficiency letter of July 10, 1997, an amendment is submitted herewith to the above referenced ANDA.

The Agency's deficiency letter of July 10, 1997 is included as Attachment #1. Each deficiency item enumerated in the Agency's letter is shown in **RECEIVED** box and has been addressed in the sequence that it was presented.

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UPSHER-SMITH

GENERIC DRUGS

1. The single-dose fasting study, and the single-dose fed/fasted study have been found incomplete as no long term stability data was submitted on the analytes stored in frozen plasma. Stability data should be submitted on each analyte (pentoxifylline, MI and MV) stored in frozen plasma over a period of time equivalent to the longest time between first sample withdrawal, and final sample analysis, and at the temperature at which the frozen samples were actually stored in the bioequivalence studies.

Long term stability data has been collected and analyzed by [redacted] laboratories as a validation of their analytical method. The report of this stability data is submitted herewith as Attachment #2.

A measure of the extended stability of pentoxifylline and its metabolites, M-I and M-V in human plasma at -20°C using both the [redacted] and [redacted] methods has been completed. A pool of human plasma was fortified with the analytes on May 10, 1996, aliquotted and stored at -20°C . These samples were then analyzed using [redacted] July 14, 1997. The [redacted] samples were evaluated at concentrations of 10.0, 100, and 400 ng/ml for pentoxifylline, 20.0, 200, and 800 ng/ml for M-I, and 50.0, 500, and 2000 ng/ml for M-V. A pool of human plasma was fortified with the analytes on August 19, 1996, aliquotted and stored at -20°C . These samples were then analyzed using [redacted] on July 16, 1997. The [redacted] samples were evaluated at concentrations of 2.00, 3.00, and 5.00 ng/ml for pentoxifylline, 4.00, 6.00, and 10.0 ng/ml for M-I, and 10.0, 15.0, and 25.0 ng/ml for M-V. The analysis of all of these samples against a freshly prepared calibration curve showed no significant degradation for pentoxifylline or its metabolites in human plasma under these conditions.

2. The multiple dose, fasting study has been found unacceptable by the Division of Bioequivalence (DBE) for the following reasons:
 - a. The data for pentoxifylline showed that the C_{max} values for 10 out of 25 subjects (#'s 1, 5, 6, 11, 12, 13, 14, 15, 22, and 25) during test and/or reference treatment were the first non-zero concentrations. DBE has found that this particular situation results in undependable results; therefore, data from these 10 subjects were deleted and the statistics were recalculated by the reviewer. The 90% confidence interval for the log-transformed C_{max} was 94.4-132.2. DBE considers these results to be unacceptable for use in bioequivalence determination. For future studies, consider adding a sampling time at 0.25 hour.

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Upsher-Smith believes that the removal of 10 subjects from the statistical analysis for pentoxifylline is unjustified for two reasons. First, additional pharmacokinetic evaluations of the multiple dose, steady state, study data has shown that the Cmax value at the first non-zero timepoint (0.5 hour) accurately reflects the maximum concentration obtained during the sampling period. Secondly, Upsher-Smith used the sampling profile recommended by the FDA.

Upsher-Smith has performed additional pharmacokinetic analyses on the data to show that the maximum concentration was not underestimated in the multiple dose study. In the steady-state interval, the first post-dose sample was obtained at 0.5 hours, and the maximum pentoxifylline concentration was observed at 0.5 hours for thirteen out of fifty doses (25 subjects, Test and Reference).

Two approaches have been used to evaluate whether the true maximum concentration was accurately estimated in the multiple dose study. One was a modeling approach, whereby single dose data (single dose, fasted study) were fitted to the model and then concentrations during a steady-state interval were predicted from the model. The number of subjects for whom the maximum concentration would have been observed in a sample obtained before the 0.5 hour sample was counted, and the difference between this maximum concentration and the 0.5 hour concentration was calculated. Thus, the extent to which the maximum concentration was underestimated by the sampling plan used in the multiple dose bioequivalence study could be evaluated.

The maximum calculated pentoxifylline concentration was observed at 0.25 hours for two subjects and at 0.5 hours for eight subjects. The remaining subjects had maximum calculated concentrations at 0.75 hour or greater. For the two cases in which the 0.25 hour concentration was the maximum, the second highest concentration was at 0.5 hours. In neither case was the 0.5 hour concentration more than 5% lower than the 0.25 hour concentration. Such a difference is within acceptable analytical error and the concentration observed at 0.5 hours could be considered a valid estimate of the maximum concentration. Thus, it has been demonstrated that even if a 0.25 hour sample were obtained during a steady-state dosing interval, a 0.5 hour sample is a valid estimate of Cmax. For the large majority of subjects, the maximum concentration during a steady-state interval would occur at 0.5 hours or later. A more detailed summary can be found in Attachment # 3 with associated graphs and tables in Attachment # 4.

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