

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-962

ADMINISTRATIVE

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 74-962 Date of Submission: April 30, 1997

Applicant's Name: Upsher-Smith Laboratories, Inc.

Established Name: Pentoxifylline Extended-release Tablets,
400 mg

Proprietary Name: Pentoxil™

Labeling Deficiencies:

1. GENERAL COMMENT:

The CDER Labeling and Nomenclature Committee has reviewed your proposed proprietary name, Pentoxil™, and has no reason to find it unacceptable.

2. INSERT

a. DESCRIPTION

- i. "structural formula" rather than "chemical structure".
- ii. Delete "g" from the MW.

b. CLINICAL PHARMACOLOGY

- i. Please reduce the prominence of the subsection title "Pharmacokinetics and Metabolism" such that it is in accord with the other subsection titles.
- ii. Pharmacokinetics and Metabolism, Fourth paragraph
 - A) First sentence - ... of the 400 mg controlled release pentoxifylline tablet, plasma ...
 - B) Add the following text after the first sentence:

... of time. Coadministration of pentoxifylline extended-release tablets with meals resulted in an increase in mean C_{max} and AUC by about 28% and 13% for pentoxifylline, respectively. C_{max} for metabolite M¹ also increased by about 20%.

Please revise your insert labeling, as instructed above, and submit final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-962 Date of Submission: September 17, 1996

Applicant's Name: Upsher-Smith Laboratories, Inc.

Established Name: Pentoxifylline Extended-release
Tablets, 400 mg

Labeling Deficiencies:

1. GENERAL COMMENT

We note you are proposing Pentoxil™ as the proprietary name of this product. Your proposal has been submitted to the CDER Labeling and Nomenclature Committee for their review and comment. We defer comment on this issue until we have received their comments. We will inform you of their response when received.

2. CONTAINER (100s, 500s and 5000s)

Relocate "TAKE WITH MEALS" to the main panel.

3. UNIT DOSE CARTON (100s)

a. See comment under CONTAINER.

b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child resistant container, e.g.,:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[Note: The second sentence is optional.]

4. INSERT

a. The requirements of 21 CFR 201.10(g) must be met. The established name must appear in certain sections in association with the proprietary name.

Please revise your labeling accordingly.

b. DESCRIPTION

- i. The CAS registry number may be deleted.
- ii. Revise the chemical name to read 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione.
- iii. Include the molecular weight - 278.31.
- iv. Include the molecular formula - $C_{13}H_{18}N_4O_3$.
- v. Inactive Ingredients - We note that you have not listed polyethylene glycol nor polysorbate 80 in your listing of inactive ingredients but have utilized the statement "and other ingredients". The USP reserves this statement for ingredients whose identity is a trade secret. If you have elected not to mention these inactive ingredients because they are a trade secret, you should use the phrase "and other ingredients", and provide supporting data concerning the "trade secret".

c. CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

- i. Paragraph three, line 18 - ...pentoxifylline has not been...
- ii. Paragraph four - Replace "extended" with "controlled". [2 places]

d. PRECAUTIONS

- i. In the fourth sentence of the General subsection and the second sentence of the Drug Interactions subsection, revise "Warfarin" to read "warfarin".
- ii. Delete "tablets" from "pentoxifylline" in the "General" and "Drug Interactions" subsections.
- iii. General, third sentence - ...placebo, but, as it is a...

- iv. Carcinogenesis, Mutagenesis and Impairment of Fertility - Delete "and" from the title and revise to read as follows:

...weight; 1.5 times the MRHD in....and 3.3 times the MRHD in the rat...

v. Pregnancy

- i. Revise the subsection heading to read as follows:

**Pregnancy: Teratogenic Effects:
Pregnancy Category C.**

- ii. Delete the first sentence and insert the following text:

Teratogenicity studies have been performed in rats and rabbits, using oral doses up to 576 and 264 mg/kg, respectively. On a weight basis, these doses are 24 and 11 times the maximum recommended human dose (MRHD); on a body-surface-area basis, they are 4.2 and 3.5 times the MRHD. No evidence...

e. ADVERSE REACTIONS

Delete "Pentoxifylline" from the title and replace "Active" in the column headings with "Pentoxifylline".

f. OVERDOSAGE

- i. Make the following revision in the first sentence, "...with pentoxifylline has been...".
- ii. Let the penultimate sentence, "In addition...", begin a new paragraph.

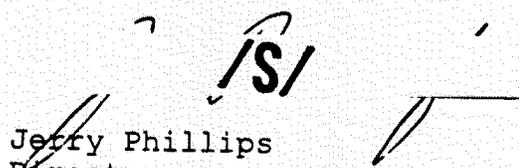
g. HOW SUPPLIED

Describe the scoring of your tablet, e.g., "Pink, unscored, ...".

Please revise your container labels, unit-dose carton and insert labeling, as instructed above, and submit final printed container and unit dose labels, carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Jerry Phillips
Director
Division of Labeling and Program Support
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TELEPHONE MEMO

To: Cindy Farner
Upsher-Smith

REF # ANDA 74-962

From: Lizzie Sanchez

Date: January 6, 1999

Subject: Pentoxifyline- First time point Cmax

Requested by: Doug Sporn

Ms. Farner was contacted to inform her that the Division of Bioequivalence has reevaluated the practice of deleting subjects whose first-time point was Cmax, from the statistical analysis. From now on it is being discontinued. A letter to the firm was sent on January 13, 1998 stating that the multiple dose study has failed due to this practice. Upsher Smith has already finished a multiple dose study to address the deficiency. Since this was the only deficiency, the Division can revise the review of the study and issue acceptable comments. She was advised that it is up to them if they want to send the new study, they do not have to send it.

TELEPHONE MEMO

To: Cindy Farner
Upsher-Smith

REF # ANDA 74-962

From: Lizzie Sanchez

Date: January 6, 1999

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ANDA APPROVAL SUMMARY

ANDA # 74-962

DRUG PRODUCT: Pentoxifylline ER Tablets, 400 mg

FIRM: Upsher-Smith

DOSAGE FORM: Tablets

STRENGTHS: 400 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

The drug product will be manufactured and packaged at:

Upsher-Smith laboratories, Inc.

Minneapolis, MN 55447

Raw material, in-process, finished product and stability testing performed at:

Upsher-Smith Laboratories, Inc.

Minneapolis, MN 55441

(OK on 2-12-99).

Manufacturer-Active Ingredients:

The drug substance pentoxifylline is manufactured by:

(OK on 2-2-99).

Contract Laboratories:

The following outside firms are listed for this ANDA:

nc.

(OK on 2-1-99).

Performs testing on raw materials

Performs microbial testing on purified water

(EES: Pending)

Performs microbial testing on magnesium stearate

..

All acceptable 3/22/99.

BIO STUDY:

Satisfactory reviewed on 1-28-99 per J. Chaney.

400 mg

: Tablets (executed batch #61037), used :s a
source of drug substance).

Pentoxifylline Extended Release 400 mg tablet, lot #61037,
comparing it to Hoechst-Russel's Trental 400 mg tablet, lot
#0780665 found acceptable by J. Chaney.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Satisfactory

Since the drug substance and finished drug product are not USP
items, methods validation for both is required.

Method validation for samples of the active ingredient and finished
product were sent to Detroit District Laboratory on 10-14-97 by Don
Shostak and found acceptable on 3-15-99.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN
CONTAINER SECTION?:

Stability protocol: Satisfactory

Expiration date:

24 months expiration date with 3 month accelerated (40°C/75% RH)
stability data was submitted for test batch lot # 61037 packaged in
the proposed market containers, i.e., bottles of 100, 500 and 5000
tablets and unit dose blister packs.

3 and 6 month room temperature data was submitted for the 100 and
500 tablet bottles and the unit dose blister pack and 3 month data
for the 5000 tablet bottle. (12 month room temperature data was
submitted in the 4/30/97 amendment).

LABELING:

Satisfactory A Vezza reviewed on 12/5/97

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

400 mg

Tablets (executed batch #61037), used as a source of drug substance).

: was reviewed and found acceptable by L. Tang, on 1-25-99.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

400 mg

Tablets (executed batch #61037), used Ltd. as a source of drug substance).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch (blank batch):

400 mg

Tablets (blank batch size).

HEMIST: Lucia C. Tang

DATE: 3-17-99

SUPERVISOR: Ubrani Venkataram

DATE: 3-19-99

F/T by pah/3/23/99

/S/

5/24/99

74962AAP.P/Tang/3-17-99