

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-962

BIOEQUIVALENCE REVIEW(S)

JAN 13 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-962

APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Pentoxifylline Extended Release Tablets, 400 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

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(1989)
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1. Your comments in defense of the Cmax data presented in this amendment are based largely on simulations, predictions, and other hypothetical data which cannot serve as the basis for a regulatory decision. The Division's decision is unchanged and the multiple dose study conducted Pentoxifylline Extended Release 400 mg Tablet, lot #61037, comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665, remains unacceptable. The multiple dose study should be repeated with earlier sampling.
 2. The new dissolution testing conducted by you on your Pentoxifylline Extended Release 400 mg Tablet has been found acceptable. Your proposed dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 1 (basket) at 100 rpm. The test product should meet the following tentative specifications:

Also, the Division of Bioequivalence requests that you submit dissolution data on the reference product using the proposed method.

Sincerely yours,

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Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3' / *Handwritten initials*

ANDA: 74-962 APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Pentoxifylline ER Tablets, 400 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Based on the data submitted, the following dissolution testing is recommended for your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 1 (basket) at 100 rpm. The test product should meet the following interim specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Handwritten signature

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:

HFD-652/ J. Chaney
HFD-652/ Y. Huang *YH 1/26/99*
HFD-617/ Elaine Hu
HFD-650/ D. Conner *DA 1/28/99*

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BIOEQUIVALENCY - ACCEPTABLE Submission date: 9/8/97

DISSOLUTION DATA (DIS)

Strengths: 400 mg

Outcome: **AC** **IC** **UN** **NC**

NOTE:

AC - Acceptable
NC - No Action

UN - Unacceptable
IC - Incomplete

OUTCOME DECISIONS: Acceptable

WINBIO COMMENTS:

The bioequivalence studies and dissolution testing have been found acceptable.

ANDA: 74-962 APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Pentoxifylline ER Tablets, 400 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Based on the data submitted, the following dissolution testing is recommended for your stability and quality control programs:

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Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA # 74-962 SPONSOR: Upsher-Smith Laboratories, Inc.

DRUG & DOSAGE FORM: Pentoxifylline Extended Release Tablets

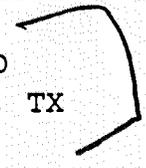
STRENGTH: 400 mg

TYPE OF STUDY: Fasting, fed and multiple dose Bioequivalence studies, and dissolution data

STUDY SITES:

CLINICAL: PRACS Institute, Fargo, ND

ANALYTICAL: CEDRA Corporation, Austin, TX



STUDY SUMMARY:
Acceptable (See Review)

DISSOLUTION:
Acceptable (See Review)

PRIMARY REVIEWER: James E. Chaney, Ph.D. BRANCH: I
INITIAL: JS/ DATE: 1/26/99

BRANCH CHIEF: Yih Chain Huang, Ph.D. BRANCH: I
INITIAL: JS/ DATE: 1/26/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: JS/ DATE: 1/28/99

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ DATE: _____

Pentoxifylline
400 mg Extended
Release Tablets
ANDA #74-962
Reviewer: J. Chaney

Upsher-Smith
Laboratories, Inc.
Minneapolis, MN
Submission Dates:
January 15, 1999

Addendum to Review of the in vivo Bioequivalence Studies and Amended Dissolution Studies

The Division of Bioequivalence has reevaluated the current practice of deleting subjects whose first time-point is C_{max} , from the statistical analysis. This practice has been discontinued. The status of bioequivalence reviews are being changed from unacceptable to acceptable if the only outstanding deficiency is that C_{max} values are the first nonzero concentrations. The firm has been contacted by phone and informed that the reviews will be modified to reflect this change.

The Division's decision has changed and the multiple dose study conducted on Pentoxifylline Extended Release 400 mg Tablet, lot #61037, comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665, has been found acceptable.

The Division of Bioequivalence in its January 13, 1998 letter requested the firm to submit data on the reference product biolot using the firm's most recent proposed dissolution testing method.

The requested dissolution data on the reference product was submitted on January 15, 1999 and is shown in Table 1. However, the data was generated from a lot different from that used in the biostudy because the biostudy lot had expired.

This dissolution testing conducted on the reference product Pentoxifylline Extended Release 400 mg Tablet is acceptable.

Recommendations

1. The in vivo single dose fasting and nonfasting bioequivalence studies and the multiple dose study conducted by Upsher-Smith Laboratories, Inc., on its Pentoxifylline Extended Release 400 mg Tablet, lot

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
 Dose Strength: 400 mg
 ANDA No.: 74-962
 Firm: Upsher-Smith Labs
 Submission Date: 9/8/97
 File Name: 74962ad.199

I. Conditions for Dissolution Testing:

USP XXIII Basket at 100 RPM No. Units Tested: 12
 Medium: Deionized Water; Volume: 900 mL
 Specifications:

Reference Drug: Hoechst-Roussel's Trental[®] 400 mg
 Extended Release Tablets
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sample Times (Hr)	Reference Product Lot # 0780665			Test Product (Biostudy) Lot # 61037		
	Mean	Range	%CV	Mean	Range	%CV
2	23.8		3.6	26.6		6.1
8	61.0		2.0	64.4		2.2
12	78.2		1.2	83.3		5.3
20	96.7		0.8	100.8		3.6

#61037, comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665, has been found acceptable by the Division of Bioequivalence. The studies demonstrate that Upsher-Smith Laboratories' Pentoxifylline Extended Release 400 mg Tablets are bioequivalent to the reference product Trental 400 mg tablet manufactured by Hoechst-Roussel.

2. The dissolution testing has been found acceptable. The dissolution testing should be conducted in 900 mL of deionized water at 37 C using USP 23 apparatus 1 (basket) at 100 rpm. The following specifications are recommended:

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James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

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Date 1/26/99

Concur: *IS/*

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date 1/28/99

Pentoxifylline
 400 mg Extended Release Tablets
 ANDA #74-962
 Reviewer: J. Chaney

Upsher-Smith Laboratories, Inc.
 Minneapolis, MN
 Submission Date:
 September 8, 1997

**Review Of An Amendment To The *in vivo* Bioequivalence
 And Dissolution Studies Submitted September 17, 1996**

1. Deficiency Comment #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.

Sponsor's Response: 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 *in vivo* and *in vitro* analytical methods has been completed. 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 (Tables 1 and 2).

Table 1. Concentrations (ng/ml) Determined Using after Storage (-20°) for 14 Months					
Found	% Dev.	Found	% Dev.	Found	% Dev.
Parent					
Initial 400 ng/mL		Initial 100 ng/mL		Initial 10.0 ng/mL	
429	7.3	106	6.0	10.8	8.0
420	5.0	109	9.0	11.9	19.0
426	6.5	106	6.0	12.1	21.0
Mean % Dev = 6.3		Mean % Dev. = 7.0		Mean % Dev. = 16.0	
MI					
Initial 800 ng/mL		Initial 200 ng/mL		Initial 20.0 ng/mL	
865	8.1	213	6.5	19.9	-0.50
842	5.3	219	9.5	23.1	15.5
857	7.1	210	5.0	24.5	22.5
Mean % Dev. = 6.8		Mean % Dev. = 7.0		Mean % Dev. = 12.5	

(Continuation of Table 1)					
MV					
Initial 2000 ng/mL		Initial 500 ng/mL		Initial 50.0 ng/mL	
1610	-19.5	499	-0.20	47.3	-5.4
2000	0.00	520	4.0	51.4	2.8
1510	-24.5	490	-2.0	52.5	5.0
Mean % Dev. = -14.7		Mean % Dev. = 0.60		Mean % Dev. = 0.80	

Table 2. Concentrations (ng/ml) Determined after Storage (-20°) for 11 Months					
Found	% Dev.	Found ng/mL	% Dev.	Found ng/mL	% Dev.
Parent					
Initial 5.00 ng/mL		Initial 3.00 ng/mL		Initial 2.00 ng/mL	
4.72	-5.6	2.88	-4.0	2.04	2.0
4.65	-7.0	2.92	-2.7	1.90	-5.0
4.40	-2.0	2.90	-3.3	1.00	-0.50
Mean % Dev = -8.2		Mean % Dev. = -3.3		Mean % Dev. = -1.2	
MI					
Initial 10.0 ng/mL		Initial 6.00 ng/mL		Initial 4.00 ng/mL	
9.74	-2.6	5.70	-5.0	4.16	4.0
9.38	-6.2	6.61	10.2	4.14	3.5
9.24	-7.6	6.32	5.3	4.24	6.05
Mean % Dev. = -5.5		Mean % Dev. = 3.5		Mean % Dev. = 4.5	
MIV					
Initial 25.0 ng/mL		Initial 15.0 ng/mL		Initial 10.0 ng/mL	
25.1	0.40	14.5	-3.3	11.0	10.0
24.3	-2.8	15.3	2.0	11.3	13.0
23.7	-5.2	15.2	1.3	11.1	11.0
Mean % Dev. = -2.5		Mean % Dev. = 0.00		Mean % Dev. = 11.3	

Reviewer's Comments: The firm has demonstrated stability of the drug product stored in frozen plasma under the conditions actually used in the bioequivalence study over periods of time (11 and 14 months) exceeding the length of time the bioequivalence study samples were actually stored (six months or less).

Deficiency Comment #2a

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Page(s) 5

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

Extended Release Tablets (Lot #61037) is acceptable.

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
 Dose Strength: 400 mg
 ANDA No.: 74-962
 Firm: Upsher-Smith Labs
 Submission Date: 9/8/97
 File Name: 74962sd.996

I. Conditions for Dissolution Testing:

USP XXIII Basket: X Paddle: RPM: 100 No. Units Tested: 12
 Medium: Deionized Water; Volume: 900 mL
 Specifications:

Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sample Times (Hr)	Dissolution data from the test biostudy lot # 61037 (2X6 tablets)			Combined dissolution data from the test biostudy lot (2X6 tablets) and the 6 tablets from each of 7 different trial lots using the revised method.		
	Mean	Range	%CV	Mean	Range	%CV
2	26.6		6.1	26.3		1.1
8	64.4		2.2	64.9		1.3
12	83.3		5.3	83.6		2.6
20	100.8		3.6	100.0		2.5

Deficiency

The firm's comments in defense of their Cmax data presented in this amendment are based largely on simulations, predictions, and other hypothetical data which cannot serve as the basis for a regulatory decision. The Division's decision is unchanged and the multiple dose study remains unacceptable. The multiple dose study should be repeated with earlier sampling.

Recommendations

1. The bioequivalence study (multiple dose, fasting conditions) conducted by Upsher-Smith Laboratories, Inc. on its Pentoxifylline Extended Release 400 mg Tablet, lot #61037, comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665, has been found unacceptable by the Division of Bioequivalence due to deficiency #1.
2. The dissolution testing conducted by Upsher-Smith Laboratories, Inc. on its Pentoxifylline Extended Release 400 mg Tablet has been found acceptable. The firm's proposed dissolution testing should be incorporated into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 1 (basket) at _____ pm. The test product should meet the following tentative specifications:

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Also, the Division of Bioequivalence requests the firm to submit dissolution data on the reference product.

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James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

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1/9/98

Concur: _____
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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[Signature]

Date 1/9/98

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BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-962 APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Pentoxifylline Extended Release Tablets, 400 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your comments in defense of the Cmax data presented in this amendment are based largely on simulations, predictions, and other hypothetical data which cannot serve as the basis for a regulatory decision. The Division's decision is unchanged and the multiple dose study conducted Pentoxifylline Extended Release 400 mg Tablet, lot #61037, comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665, remains unacceptable. The multiple dose study should be repeated with earlier sampling.
2. The new dissolution testing conducted by you on your Pentoxifylline Extended Release 400 mg Tablet has been found acceptable. Your proposed dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 1 (basket) at rpm. The test product should meet the following tentative specifications:

Also, the Division of Bioequivalence requests that you submit dissolution data on the reference product using the proposed method.

Sincerely yours,

/s/ -

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research