CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074425

Trade Name : PENTOXIFYLLINE EXTENDED RELEASE TABLETS 400MG

Generic Name: Pentoxifylline Extended Release Tablets 400mg

Sponsor : Mylan Pharmaceuticals, Inc.

Approval Date: July 8, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074425

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074425

APPROVAL LETTER

ANDA 74-425

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

JUL 8 1997

Dear Mr. Sisto:

This is in reference to your abbreviated new drug application dated November 19, 1993, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Pentoxifylline Extended-release Tablets, 400 mg.

Reference is also made to your amendments dated October 14, 1996, February 17, May 8, and July 7, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Pentoxifylline Extended-release Tablets, 400 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Trental® Tablets, 400 mg of Hoechst Marion Roussel Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application. The "interim" dissolution test(s) and tolerances are:

Dissolution - 2 hours =
8 hours =
12 hours =
24 hours =

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70 (c) (1) when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under 21 CFR 314.70 (b) (2) (ii).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

7/8/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

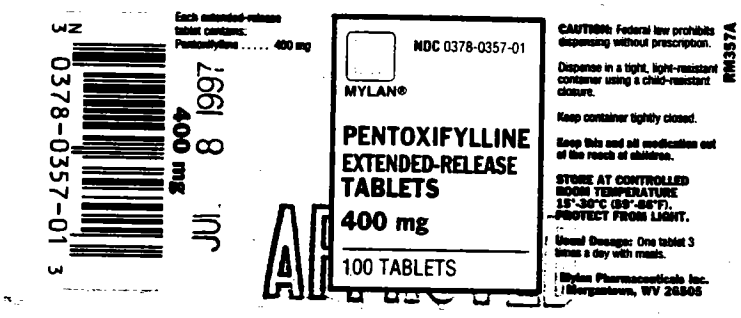
APPLICATION NUMBER 074425

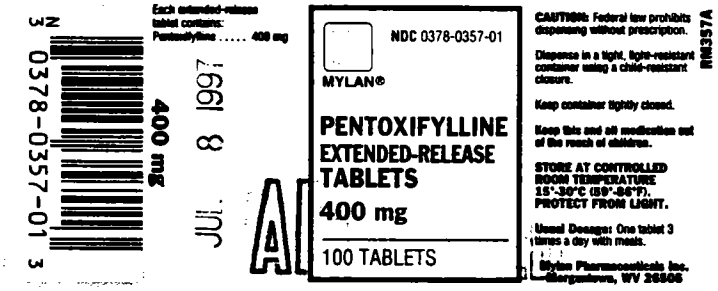
FINAL PRINTED LABELING

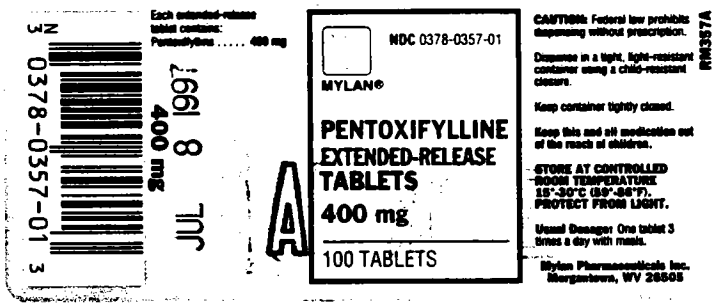
MARKU
N/AC FPL

MYLAN PHARMACEUTICALS INC.

PENTOXIFYLLINE EXTENDED RELEASE
TABLETS, 400 MG
ANDA 74-425







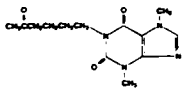
PENX:R2

JUL 8 1997

PENTOXIFYLLINE EXTENDED-RELEASE TABLETS 400 mg

DESCRIPTION: Each extended-release tablet, for oral administration, contains 400 mg of pentoxifylline. In addition, each tablet contains the following inactive ingredients: hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, titanium dioxide, triacetin, D&C Red #30 Aluminum Lake, FD&C Blue #2 Aluminum Lake, and FD&C Yellow #6 Aluminum Lake in a controlled-release formulation. Pentoxifylline is a trisubstituted xanthine derivative designated chemically as 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione that, unlike theophylline, is a hemorrheologic agent, i.e. an agent that affects blood viscosity. Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene.

The chemical structure is:



$C_{13}H_{18}N_4O_3$
M.W. 278.31

CLINICAL PHARMACOLOGY:
Mode of Action: Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leu-

disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leukocyte properties of hemorrheologic importance have been modified in animal and *in vitro* human studies. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease.

Pharmacokinetics and Metabolism: After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing. Peak plasma levels of the parent compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxyhexyl]-3,7-dime-thylxanthine) and Metabolite V (1-[3-carboxypropyl]-3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than pentoxifylline.

Following oral administration of aqueous solutions containing 100 to 400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose-related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4 to 0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (Cytochrome P_{450}) following multiple oral doses.

Excretion is almost totally urinary: the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces. Food intake shortly before dosing delays absorption of an immediate release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of pentoxifylline have not been studied in patients with renal and/or hepatic dysfunction, but

tions in plasma levels of parent compound and its metabolites. the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces. Food intake shortly before dosing delays absorption of an immediate release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of pentoxifylline have not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years).

After administration of a 400 mg pentoxifylline extended-release tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2 to 4 hours and remain constant over an extended period of time. The controlled release of pentoxifylline from the tablet eliminates peaks and troughs in plasma levels for improved gastrointestinal tolerance.

INDICATIONS AND USAGE: Pentoxifylline extended-release tablets are indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Pentoxifylline can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS: Pentoxifylline extended-release tablets should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS: General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Pentoxifylline has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that pentoxifylline causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including hematocrit and/or hemoglobin.

on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including hematocrit and/or hemoglobin.

Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with pentoxifylline with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Pentoxifylline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifylline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to 450 mg/kg (approximately 19 times the maximum recommended human daily dose [MRHD] in both species when based on body-weight; 1.5 times the MRHD in the mouse and 3.3 times the MRHD in the rat when based on body-surface area). In mice, the drug was administered for 18 months, whereas in rats, the drug was administered for 18 months followed by an additional 6 months without drug exposure. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females of the 450 mg/kg group. The relevance of this find-

ing to human use is uncertain. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) and in cultured mammalian cells (unscheduled DNA synthesis test) when tested in the presence and absence of metabolic activation. It was also negative in the *in vivo* mouse micronucleus test.

Pregnancy: *Teratogenic Effects:* *Category C:* 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 of fetal malformation was observed. Increased resorption was seen in rats of the 576 mg/kg group. There are no adequate and well controlled studies in pregnant women. Pentoxifylline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Clinical trials were conducted using either extended-release pentoxifylline tablets for up to 60 weeks or immediate-release pentoxifylline capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200 to 400 mg tid.

The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received extended-release pentoxifylline tablets, immediate-release pentoxifylline capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the extended-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects. (See table.)

INCIDENCE (%) OF SIDE EFFECTS

	Extended Release Tablets	Immediate-Release Capsules Used only for

tients discontinued because of adverse effects. (See table.)

INCIDENCE (%) OF SIDE EFFECTS

	Extended Release Tablets Commercially Available		Immediate-Release Capsules Used only for Controlled Clinical Trials	
	Pentoxifylline	Placebo	Pentoxifylline	Placebo
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	-	1.1	2.2
Arrhythmia/Palpitation	-	-	1.7	0.7
Flushing	-	-	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	-	-	4.0	1.4
Belching/Flatus/Bloating	0.6	-	9.0	3.6
Diarrhea	-	-	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	-	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	-	-	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	-	-	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	-	-	2.3	2.2
Tremor	0.3	0.8	-	-
Blurred Vision	-	-	2.3	1.4

Pentoxifylline has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:

Cardiovascular: dyspnea, edema, hypotension.

Digestive: anorexia, cholecystitis, constipation, dry mouth/thirst.

Nervous: anxiety, confusion, depression, seizures.

Respiratory: epistaxis, flu-like symptoms, laryngitis, nasal congestion.

Skin and Appendages: brittle fingernails, pruritus, rash, urticaria, angioedema.

Special Senses: blurred vision, conjunctivitis, earache, scotoma.

Miscellaneous: bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: *Cardiovascular*–angina, arrhythmia, tachycardia, anaphylactoid reaction; *Digestive*–hepatitis, jaundice, increased liver enzymes; and *Hemic and Lymphatic*–decreased serum fibrinogen, pancytopenia, aplastic anemia, leu-

Miscellaneous: bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: *Cardiovascular*–angina, arrhythmia, tachycardia, anaphylactoid reaction; *Digestive*–hepatitis, jaundice, increased liver enzymes; and *Hemic and Lymphatic*–decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

OVERDOSAGE: Over dosage with pentoxifylline has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4 to 5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.

In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to absorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION: The usual dosage of pentoxifylline in extended-release tablet form is one tablet (400 mg) three times a day with meals.

While the effect of pentoxifylline may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.

Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of pentoxifylline should be discontinued.

HOW SUPPLIED: Pentoxifylline Extended-release Tablets are available as film coated, lavender, unscored, capsule-shaped tablets, each containing 400 mg of pentoxifylline. The tablet is marked with MYLAN on one side and 357 on the other side. It is available as follows:

NDC 0378-0357-01
bottles of 100 tablets

STORE AT CONTROLLED ROOM TEMPERATURE

are dose related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of pentoxifylline should be discontinued.

HOW SUPPLIED: Pentoxifylline Extended-release Tablets are available as film coated, lavender, unscored, capsule-shaped tablets, each containing 400 mg of pentoxifylline. The tablet is marked with MYLAN on one side and 357 on the other side. It is available as follows:

NDC 0378-0357-01
bottles of 100 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container using a child-resistant closure.

Caution: Federal law prohibits dispensing without prescription.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED DECEMBER 1996
PENX:R2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074425

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-425

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals, Inc.
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS for ANDA SUBMISSION
The firm certifies that to the best of their knowledge the referenced product is covered by patent numbers 4189469 and 3737433 which expire 2/2/97 and 4/3/97, respectively. The firm also certifies that the referenced product is covered by a new chemical entity (NCE) exclusivity which expired on 8/30/94. The firm will market upon approval of the application and expiration of patent numbers 4189469 and 3737433 and the NCE exclusivity period.

Innovator: Hoechst Roussel - Trental®.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Pentoxifylline

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
- 11/19/93 - Original.
- 12/21/93 - Response to refuse to file.
- 4/17/96 - Response to 1st def. letter (chem. & labeling).
- 10/14/96 - Response to 1st Bio. Letter.
- 2/17/97 - Response to 2nd def. letter (chem. & labeling). Subject of this review.
- 4/14/97 - O/NC, regarding method validation.
- 5/8/97 - Response to 2nd Bio. def. letter. Dissolution specifications and revised finished product and stability. Subject of this review.

FDA:
- 12/14/93 - Refuse to file, need comparative dissolution data.
- 1/28/94 - Acknowledgment.
- 6/3/94 - 1st def. letter (chem. & labeling).
- 10/17/94 - 1st Bio. def. letter.
- 12/2/96 - 2nd def. letter (chem. & labeling).

5/1/97 - 2nd Bio. def. letter.

10. PHARMACOLOGICAL CATEGORY
Vasodilator

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

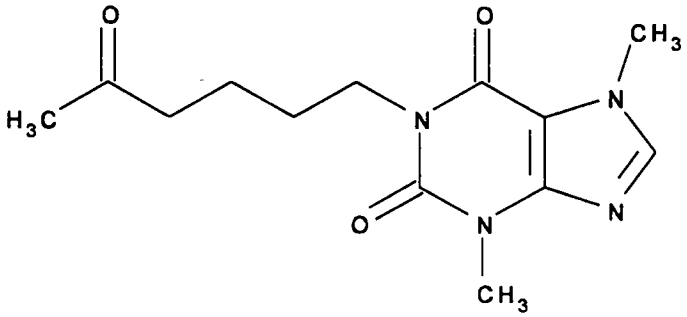
13. DOSAGE FORM
Extended-release Tablet

14. POTENCY
400 mg

15. CHEMICAL NAME AND STRUCTURE

Pentoxifylline

$C_{13}H_{18}N_4O_3$; M.W. = 278.31



3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione.
CAS [6493-05-6]

16. RECORDS AND REPORTS
None

17. COMMENTS

a. Method Validation:

Sent to Baltimore District Laboratory on 5/15/97.

b. Bioequivalence Status:

Pending review, assigned to Hoainhon Nguyen on 5/15/97.

DMF's, EER, and labeling satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER: Norman R. Gregory

DATE COMPLETED: 5/19/97 (chem.)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074425

BIOEQUIVALENCE REVIEW(S)

ANDA 74-425

JUN 20 1997

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown WV 26504-4310

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Pentoxifylline Extended-release Tablets, 400 mg.

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

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of SGF without enzyme at 37°C using USP 23 apparatus II(paddle) at 50 rpm.

Sampling Schedule	Limits
2 hours	
8 hours	
12 hours	
24 hours	

Note to Mylan Pharmaceuticals and

In the future, for analytical method validation, the concentrations of the quality controls should be chosen approximately within the concentration range of the actual sample plasma concentrations in order for the assay to be considered fully validated.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 13 1997

Pentoxifylline ER Tablets, 400 mg
ANDA # 74-425
Reviewer: Hoainhon Nguyen
WP # 74425a.597

Mylan Pharmaceuticals
Morgantown, WV
Submission Date:
May 8, 1997

Review of a Study Amendment

The firm has submitted a study amendment in response to the Division of Bioequivalence's Deficiency Comments in the letter dated May 1, 1997.

Deficiencies:

1. *The repeat single-dose, fasting bioequivalence study:*

In the Repeat Single-Dose Fasting Study, there were many subjects without AUC(0-Inf) calculated for each analyte, and several subjects with only 2 points used for calculating the terminal slope. Please provide the SOP for the determination of the individual elimination rate constant.

2. *The repeat multiple-dose, fasting bioequivalence study:*

b.

3. *There are no further questions on the non-fasting single-dose bioequivalence study.*

4. *Since the Repeat Multiple-Dose study and the non-fasting study were conducted on the original formulation with , and the Repeat Fasting Single-Dose study and the in vitro dissolution testing were conducted on the formulation, there is lack of in vivo or in vitro testing data comparing the original formulation with the new formulation to demonstrate that the removal of does not affect the bioavailability of the reformulated product.*

   Since the is only used for appearance, and to enhance the speed of bottle filling, a request for waiver of in vivo bioequivalence requirements would be considered. To support your request for such a waiver, in vitro dissolution data comparing the two formulations are considered sufficient bioequivalence requirement for the reformulated product in addition to the Fasting Single-Dose Study already submitted.

   We advise comparative dissolution testing between the bio-lot of the formulation and a lot of the original formulation, using the FDA-recommended dissolution procedure and specifications.

5.

0. *The in-vitro dissolution testing on Pentoxifylline ER Tablets, 400 mg, lot # 2C003B, has been found acceptable; however, the Division of Bioequivalence recommends that your proposed procedure and specifications be modified as follows:*

   a. *The dissolution testing should be incorporated into the manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of SGF without enzyme at 37 °C using USP 23 apparatus II(paddle) at 50 rpm. Since the results between the paddle speed of 50 rpm and 75 rpm (with other dissolution conditions being equal) are essentially equivalent, the lower paddle speed is preferred by the Division.*

   b. *The tentative specifications (derived from the rule that the range should be approximately ±10% of the label claim of the mean, to more closely reflect the actual observed data submitted) for the test product should be:*

Sampling Schedule	Limits
2 hours	
8 hours	
12 hours	
24 hours	

Firm's Response #1:

DBE Comment: The agency does not recommend the firm's method of determining the elimination rate constant using only two concentrations from the terminal phase. ANOVA re-analyses of log-transformed AUC(0-Inf) were performed by the reviewer excluding all Subjects with questionable elimination rate constants (that were not calculated or calculated using only two time points). The results of the re-analyses are as follows:

Log-Transformed AUC(0-Inf)

	PENT	M1	M5
90%C.I.	[0.80;1.36]	[0.87;1.05]	[0.90;1.06]
RatioT/R*	1.04	0.96	0.98
N	13	17	13

*Geometric LSMeans

The 90% confidence interval for PENT is not within the acceptable limit of [0.80;1.25]. However, the ratio of geometric means of Test to Reference for PENT is within [0.80,1.25]. In addition, number of subjects in the ANOVA re-analysis for PENT is only 13 and not sufficient for calculation of the 90% confidence interval. AUC(0-Inf) is not considered as accurate measurement of the extent of absorption as AUC(0-T) which meets the 90% confidence interval requirement.

The firm's response to DBE Deficiency Comment 1 is, therefore, considered adequate. The Repeat Fasting Study data are considered acceptable with respect to AUC(0-Infinity) and the elimination rate constants.

Firm's Response #2a: The firm has provided the statistical analysis for corrected CMAX/TMAX data for the Repeat Multiple-Dose Fasting Study.

The firm has also provided possible explanation for some trough concentrations being higher than CMAX for the metabolite M1 and M5 in study PENT-9330:

1. *The formulation was designed to exhibit modified release characteristics. At 8 hours post-dose (sampling time for troughs), the plasma drug concentrations may still be governed by the absorption phase of the controlled release character of the dosage form; thus, the trough concentrations may not be in the terminal elimination phase and the concentrations may still be high. Hence, there is high probability of observing trough concentrations higher than CPEAK.*

2.

DBE Comment: The results of the statistical re-analysis of corrected CMAX/TMAX for M1 and M5 are summarized below. (Correction is not necessary for PENT).

Table IX(Corrected)
M1 Comparative Pharmacokinetic Parameters
Multiple-Dose Study; Dose = 13x400 mg; n = 36

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
AUC_{96-104} ng.hr/ml	1572*	1686*	[0.87;0.99]	0.93
CMAX(ng/ml)	298.9*	311.1*	[0.89;1.04]	0.96
CMIN(ng/ml)	115(57)	128(64)		
TMAX (hrs)	1.86(70)	1.54(43)		
FLUCT1(%)	102(28)	95.1(23)		
FLUCT2(%)	213(44)	211(64)		

*Geometric, LS Means

Table XI(Corrected)
M5 Comparative Pharmacokinetic Parameters
Multiple-Dose Study; Dose = 13x400 mg; n = 35

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
AUC_{96-104} ng.hr/ml	5597*	6003*	[0.89;0.98]	0.93
CMAX(ng/ml)	1119*	1176*	[0.90;1.01]	0.95
CMIN(ng/ml)	383(32)	382(40)		
TMAX (hrs)	1.43(41)	1.59(57)		
FLUCT1(%)	107(26)	108(21)		
FLUCT2(%)	233(62)	257(58)		

*Geometric, LS Means

The corrected CMAX/TMAX data for M1 and M5 are acceptable. The firm's explanations concerning the high plasma concentrations of M1 and M5 at some 48-hour and 72 hour time points are judged possible and satisfactory.

Firm's Response #2b:

is summarized as follows:

DBE Comment: Taken into account the special circumstance where the Repeat Multiple-Dose Study PENT-9330 was conducted (between 03/15 and 04/26/1994) prior to the issuance of the DBE Guidance "Pentoxifylline Extended Release Tablets *In Vivo* Bioequivalency and *In Vitro* Dissolution Testing" (12/22/1995) and the firm was therefore unaware of the requirement of

Firm's Response #3: *"Mylan acknowledges that there are no further questions on the non-fasting single-dose bioequivalence study."*

DBE Comment: None

Firm's Response #4: Provided are the comparative dissolution data between the bio-lot of the formulation and a lot of the original

formulation using the FDA recommended dissolution procedure. The dissolution data are summarized below.

Drug (Generic Name): Pentoxifylline
Dose Strength: 400 mg
Submission Date: May 8, 1997

Firm: Mylan Pharmaceuticals
ANDA # 74-425

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing: FDA-recommended procedure (non-compendial)
USP XXIII Basket __ Paddle X RPM 50 Units Tested: 12
Medium: Aqueous buffer of pH 1.5 (SGF) Volume: 900 ml
Reference Drug: (Manuf.) Mylan's Formulation With
Assay Methodology: Not given
FDA-Recommended Specification:

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Hrs.)	Test Product Lot # 2C003B (Without Strength (mg) 400			Reference Product Lot # 2Z012A (With Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	20		(2.7%)	21		(2.6%)
8	50		(2.3%)	52		(2.5%)
12	67		(2.4%)	69		(2.6%)
24	100		(2.1%)	99		(1.0%)

DBE Comment:

The dissolution data are acceptable.

Firm's Response #5:

The reviewer recommends that the three bioequivalence studies, all of which were based on the same analytical method and method validation, not be rejected based solely on this overlook in selection of QC's. However, it is essential that the firm and the contracting analytical laboratory are forewarned of the future repeat mistake which would then be considered "intentional" deficient practice and should result in rejection of the related studies.

Firm's Response #6: The firm has modified the dissolution testing conditions and specifications as recommended by the agency in the last correspondence.

DBE Comment: None

DBE's Overall Comments: The firm's responses to the agency's Deficiency Comments are adequate and acceptable.

The Repeat Single-Dose Fasting Study and the Repeat Multiple-Dose Study demonstrate that the test product, Mylan's Pentoxifylline ER 400 mg Tablet, is equivalent to the reference product, Hoechst-Roussel's Trental 400 mg Tablets, in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T)(Single-Dose Study) or lnAUC(96-104)(Multiple-Dose Study) and lnAUC(0-Infinity) of PENT, M1 and M5, under fasting or steady state conditions.

The formulation and original formulation of the test product are considered equivalent as judged by their equivalent comparative dissolution data and their compositions.

Recommendations:

1. The repeat multiple-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Pentoxifylline ER Tablets, 400 mg, lot # 2Z012A, comparing it with the reference product, Trental[R] Tablets, 400 mg, lot # 0784983, has been found acceptable by the Division of Bioequivalence. The test product, Mylan's Pentoxifylline ER Tablets, 400 mg, is deemed bioequivalent to the reference product, Hoechst-Roussel's Trental Tablets, 400 mg, under steady-state conditions.

2. The repeat single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Pentoxifylline ER Tablets, 400 mg, lot # 2C003B, comparing it with the reference product, Trental[R] Tablets, 400 mg, lot # 0782965, has been found acceptable by the Division of Bioequivalence. The test product, Mylan's Pentoxifylline ER Tablets, 400 mg, is deemed bioequivalent to the reference product, Hoechst-Roussel's Trental Tablets, 400 mg, under fasting conditions.

3. The non-fasting single-dose bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Pentoxifylline ER Tablets, 400 mg, lot # 2Z012A, comparing it with the reference product, Trental[R] Tablets, 400 mg, lot # 0787652 has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Pentoxifylline ER Tablets, 400 mg, manufactured by Mylan Pharmaceuticals is bioequivalent to the reference product, Trental Tablets, 400 mg, manufactured by Hoechst-Roussel under non-fasting conditions. (See the last review dated April 25, 1997)

4. The in-vitro dissolution testing conducted by Mylan Pharmaceuticals on its Pentoxifylline ER Tablets, 400 mg, formulation and original formulation with has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900

ml of SGF without enzyme at 37°C using USP XXIII apparatus II(paddle) at 50 rpm.

The tentative specifications for the test product should be:

Sampling Schedule	Limits
2 hours	
8 hours	
12 hours	
24 hours	

5. The firm and should be informed that in the future, for analytical method validation, the concentrations of the quality controls should be chosen approximately within the concentration range of the actual sample plasma concentrations in order for the assay to be considered fully validated.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 6/10/97

Concur: _____ Date: 6/18/97
Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-425 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File , HFD-650 (Director)

Hnguyen/06-03-97/WP #74425a.597
Attachments: 2 pages

02-Jul-1996 15:40:52

Back Calculated Calibration Curve Standard Concentrations
for Pentoxifylline in Human Plasma
Nominal Concentrations ng/mL

Curve Code	STD B 5.09	STD C 10.18	STD D 50.88	STD E 153.31	STD F 508.78	STD G 746.20	STD H 915.80	STD I 1017.55
EYS07	R	10.12	50.20	152.49	523.75	770.11	911.94	984.08
EYS08	4.68	10.29	52.60	158.81	522.49	734.81	882.42	1041.68
EYS09	5.01	9.95	51.25	155.40	524.37	759.58	902.96	999.27
EYS11	4.97	9.84	52.67	157.74	490.87	780.04	952.51	959.15
EYS12	4.38	10.78	51.07	165.32	526.90	721.81	929.82	997.71
EYS13	5.45	9.51	49.41	155.70	482.07	829.90	962.05	913.70
EYS14	5.23	9.22	52.16	160.30	513.61	738.08	927.05	1002.13
EYS15	4.84	10.14	51.66	156.32	539.86	746.13	840.30	1058.55
EYS16	4.65	10.64	54.73	146.18	514.07	764.23	890.35	1022.94
EYS17	4.57	10.14	52.09	164.86	529.51	726.38	970.77	949.47
EYS18	4.85	10.46	49.43	162.57	504.40	755.51	883.78	1036.80
EYS19	5.05	11.01	51.50	142.45	479.18	755.98	924.07	1038.55
EYS20	5.16	10.44	50.12	154.37	496.75	672.22	975.14	1043.58
EYS21	C	10.22	51.81	143.27	527.90	786.37	925.12	958.01
EYS22	4.48	10.50	49.81	169.51	539.61	714.76	916.95	1002.17
EYS23	5.61	9.59	47.09	157.07	525.93	737.07	843.27	1082.17
EYS24	5.50	9.55	51.02	150.89	500.96	748.88	900.02	1040.97
EYS25	5.08	8.76	54.50	162.50	526.27	763.41	899.34	987.92
EYS26	4.10	10.54	55.67	160.84	539.98	752.27	859.88	1024.51
EYS27	5.18	9.46	52.64	152.97	534.61	731.26	925.85	995.82
EYS28	6.13	8.23	53.26	142.24	488.79	787.14	991.48	930.53
EYS29	4.93	9.68	57.02	155.71	458.71	725.64	987.17	1008.93
EYS30	4.58	10.94	50.27	158.89	512.92	751.65	914.90	1003.64
EYS31	5.81	9.08	48.19	156.29	508.60	753.22	891.02	1035.57
EYS32	4.05	11.94	49.08	158.97	543.91	751.98	903.37	984.49
EYS33	5.86	7.91	50.64	161.54	536.46	770.27	859.75	1015.36
EYS34	4.79	10.33	53.77	150.75	509.17	767.53	877.56	1033.89

PhStd 2.1-006
C - Poor Chromatography

R - Rejected

02-Jul-1996

15:40:52

Back Calculated Calibration Curve Standard Concentrations
for Pentoxifylline in Human Plasma
Nominal Concentrations ng/mL

Curve Code	STD B 5.09	STD C 10.18	STD D 50.88	STD E 153.31	STD F 508.78	STD G 746.20	STD H 915.80	STD I 1017.55
EYS36	4.30	9.97	57.05	162.75	513.62	770.04	869.02	1021.05
Mean	4.971	9.973	51.812	156.310	514.831	752.366	911.352	1006.166
SD	0.5351	0.8491	2.4529	6.9066	21.1206	28.5863	41.2818	38.7367
CV%	10.8	8.5	4.7	4.4	4.1	3.8	4.5	3.8
N	26	28	28	28	28	28	28	28
%nom	97.7	98.0	101.8	102.0	101.2	100.8	99.5	98.9

APR 25 1997

Pentoxifylline Extended-Release Tablets, 400 mg
ANDA # 74-425
Reviewer: Hoainhon Nguyen
WP # 74425sd.o96

Mylan Pharmaceuticals
Morgantown, WV
Submission Date:
October 14, 1996

Review of Bioequivalence Studies and Dissolution Data
(Including Repeat Single-Dose Fasting Study and Multiple-Dose Fasting Study)

I. Drug Information: Pentoxifylline, a synthetic xanthine derivative, is a hemorrheologic agent used for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. The drug improves the flow properties of blood by decreasing its viscosity and improving erythrocyte flexibility, and therefore increases blood flow and enhance tissue oxygenation in patients with chronic peripheral arterial disease. The drug water solubility is about 77 mg/ml at 25°C.

Pentoxifylline is rapidly and almost completely absorbed from the GI tract following oral administration, but the drug undergoes extensive first-pass metabolism in the liver. Limited data indicate that about 10-30 and 10-50% of a dose of pentoxifylline reaches systemic circulation unchanged following oral administration of extended-release tablets and conventional capsules of the drug, respectively. Initial pharmacokinetic studies using other oral dosage forms (e.g., conventional capsules) suggested that the rate but not the extent of absorption of the drug was affected by the presence of food (decrease in CMAX and increase in TMAX; no significant change in AUCs). AUCs for pentoxifylline and the 5-hydroxyhexyl metabolite increase nonlinearly with dose.

Following oral administration of an extended-release tablet, peak plasma pentoxifylline concentrations occurred within 2-4 hours and reached a plateau at 4-8 hours; peak plasma concentrations of the 5-hydroxyhexyl metabolite occurred also within 2-4 hours and reached a plateau at 4-8 hours. Plasma concentrations of the 5-hydroxyhexyl metabolite generally exceed those of pentoxifylline after 1 hour, suggesting rapid metabolism of the parent drug.

Evidence from in vitro studies indicate that pentoxifylline is 45% bound to the

erythrocyte membrane where it is rapidly metabolized to the 5-hydoxyhexyl metabolite which is about 40% bound to the membrane. Plasma concentrations of pentoxifylline and the 5-hydroxyhexyl metabolite are in equilibrium with the amounts bound to the erythrocyte membrane.

The apparent plasma half-life of pentoxifylline has been reported to be 0.4-0.8 hours following administration of immediate-release dosage forms. The drug is extensively metabolized in erythrocytes and the liver, principally via reduction, oxidation, and demethylation. The major metabolites found in blood are the 5-hydroxyhexyl and the 3-carboxypropyl derivatives; plasma concentrations of these metabolites are 5 to 8 times greater, respectively, than those of pentoxifylline. These two major metabolites are pharmacologically active and contribute to the hemorrheologic effects observed following administration of the drug; the pharmacologic potency of the 5-hydroxyhexyl metabolite is equivalent to that of the parent drug. Approximately 95% of an oral dose of the drug is excreted in urine within 24 hours, principally as metabolites. About 50-80% of an oral dose is excreted in urine as the 3-carboxypropyl metabolite and about 20% as other metabolites; only trace amounts of a dose are excreted unchanged.

Pentoxifylline is administered orally, preferably with meals. The usual adult dosage of pentoxifylline as extended-release tablets is 400 mg 3 times daily.

Adverse effects associated with the drug generally involve the GI tract and CNS, such as dyspepsia, nausea, vomiting, dizziness, headache and tremor.

Pentoxifylline is available commercially as Trental[R] extended-release, film-coated oral tablets, 400 mg, manufactured by Hoechst-Roussel.

II. <u>Bioequivalence Study Submission History</u>:

The single-dose fasting bioequivalence study and the multiple-dose fasting bioequivalence study that were submitted previously by the firm, on November 19, 1993, were found unacceptable by the Division of Bioequivalence (in the Not Approvable Letter dated October 17, 1994):

"For the Single-Dose Fasting Study (PENT-9236): For pentoxifylline, there were seven cases where the CMAX was the first non-zero concentration (at the first sampling time of 0.5 hr):

Trt. A(ref.), Subjects 8, 11, 12
Trt. B(test), Subjects 4, 7, 8, and 12

The Division considers these results to be unacceptable for use in bioequivalence determination. If these five subjects are excluded, only eight subjects remain, and the resulting 90% confidence interval for log-tranformed CMAX is 95.5-133.1% which is outside of the allowable bioequivalence interval of 80-125%."

"For the Multiple-Dose Study (PENT-9328): The Division does not accept the exclusion of data based solely on the results of a statistical test for outliers.

If ANOVA is performed including the pentoxifylline data from S16 and the Per. 2, 4.5 hr, concentration for S6, the 90% confidence intervals for log-transformed $AUC_{0\text{-}Inf.}$ and log-transformed CMAX are 81.0-96.9 and 72.9-96.8, respectively. The 90% confidence interval for log-transformed CMAX is outside of the allowable bioequivalence interval of 80-125%."

The single-dose non-fasting bioequivalence study that was submitted concurrently with the above two studies was found incomplete with a question raised by the reviewer (James Henderson) concerning the standard curves of the study: "Please explain why pentoxifylline standard curves BK011 and BK022 are both listed as Subject 5, Periods 1-3."

In this current amendment, the firm submits the results of the repeated single-dose fasting and multiple-dose fasting bioequivalence studies, and also addresses the deficiency concerning the single-dose non-fasting study. Dissolution data comparing the test with the reference product are also submitted.

It should be noted that in response to the OGD Not Approvable Letter dated June 3, 1994 concerning the use of in the formulation of the test

product. Mylan elected to delete the from the drug product, "which was added only for pharmaceutical elegance (i.e., tablet appearance) and to enhance the speed in the filling of the bottles during the packaging operation." The revised formulation was submitted to the OGD in the April 17, 1996 amendment. Mylan subsequently manufactured another biolot (Lot No. 2C003B) without and used this lot **for the repeat single-dose fasting study (PENT-9607).**

III. Repeat Bioequivalence Studies:

A. Repeat Single-Dose, Fasting Bioequivalence Study: (PENT-9607)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Mylan's pentoxifylline tablets, 400 mg, and Hoechst-Roussel's Trental® Tablets, 400 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at between May 11 and May 19, 1996. The principal investigator were Plasma samples were assayed by under the supervision of between May 31 and June 18, 1996.

Demographics:

Twenty-seven normal, healthy, non-smoking male volunteers between 18-50 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 132 - 232 lbs and 66 - 74.5 in., respectively.

Inclusion criteria:

Subjects especially did not have any history of: adverse reactions or allergy to pentoxifylline or any other xanthine (such as theophylline), any significant chronic disease, and drug and/or alcohol abuse.

Restrictions:

They were free of all medications at least 14 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed within 48 hours of their check-in appointment until their release from confinement in each period. No ingestion of any vitamins was allowed within 48 hours prior to the initial dose of the study medication. The subjects fasted for 10 hours prior to and 5 hours after each drug administration. The washout duration between the two phases was one week. Duration of confinement was approximately 11 hours pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 400 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Mylan's Pentoxifylline Tablets, 400 mg, lot # 2C003B (Batch size of units, potency of 98.7%).

Reference product: Hoechst-Roussel's Trental® Tablets, 400 mg, lot # 0782965 (Potency of 100.9%).

Blood samples were collected at predose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 30.0 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -20°C until shipping to the analytical laboratory.

Assay Methodology:

PAGES 6-10

TRADE SECRET
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Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

All twenty-seven enrolled volunteers completed the clinical portion of the study.

Subject # 27 chewed his tablet in both periods and his data were excluded from the analysis. The statistical analysis was performed using balanced 26 data sets.

A. PENT:

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity), lnCMAX, TMAX, KEL and T1/2. The results are summarized in the tables below:

Table I

PENT Comparative Pharmacokinetic Parameters
Fasting Study; Dose = 400 mg; n = 26

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	632.7*	639.7*	[0.89;1.10]	0.99
AUC (0-Inf) ng.hr/ml	886.2*	902.3*	[0.80;1.20]	0.98
CMAX(ng/ml)	103.8*	111.2*	[0.82;1.07]	0.93
TMAX (hrs)	2.18(106)	1.54(156)		
KEL (1/hrs)	0.161(58)	0.168(79)		
T1/2 (hrs)	5.75(55)	6.81(66)		

*Geometric, LS Means

Table II
Comparative Mean Plasma Levels of PENT
Fasting Study: Dose = 400 mg; n = 26
ng/ml(%CV)

Hour	Mylan	Trental[R]
0	0	0
0.25	30.7(101)	40.3(101)
0.50	72.9(63)	90.0(51)
0.75	92.0(54)	84.4(41)
1.00	76.1(45)	89.3(51)
1.50	75.5(65)	72.6(47)
2.00	62.6(53)	63.2(42)
2.50	59.4(48)	58.4(49)
3.00	53.0(50)	50.1(52)
3.50	48.4(47)	43.4(47)
4.00	46.8(68)	39.9(46)
4.50	41.6(58)	39.5(58)
5.00	37.2(59)	36.3(59)
6.00	59.1(47)	52.5(51)
7.00	57.5(65)	46.7(46)
8.00	51.5(62)	40.6(43)
10.00	34.1(52)	36.2(54)
12.00	29.5(54)	36.3(59)
16.00	21.9(87)	17.9(79)
24.00	1.38(248)	2.12(221)
30.00	0	0.333(510)
$AUC(0\text{-}T)_{ng.hr/ml}$	714(46)	688(36)
$AUC(0\text{-}Inf)_{ng.hr/ml}$	965(40)	939(34)
$CMAX_{ng/ml}$	115(48)	118(35)

B. M1:

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity), lnCMAX, TMAX, KEL and T1/2. The results are summarized in the tables below:

Table III

M1 Comparative Pharmacokinetic Parameters
Fasting Study; Dose = 400 mg; n = 26

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	1720*	1772*	[0.88;1.07]	0.97
AUC (0-Inf) ng.hr/ml	2345*	2322*	[0.91;1.11]	1.01
CMAX(ng/ml)	208.5*	206.4*	[0.91;1.12]	0.93
TMAX (hrs)	3.00(60)	2.98(94)		
KEL (1/hrs)	0.142(59)	0.172(69)		
T1/2 (hrs)	6.73(58)	6.01(79)		

*Geometric, LS Means

Table IV
Comparative Mean Plasma Levels of M1
Fasting Study; Dose = 400 mg; n = 26
ng/ml(%CV)

Hour	Mylan	Trental[R]
0	0	0
0.25	17.1(125)	24.8(106)
0.50	83.6(59)	101(55)
0.75	142(49)	146(42)
1.00	162(44)	179(46)
1.50	196(45)	204(49)
2.00	197(46)	220(51)
2.50	195(46)	204(53)
3.00	187(46)	188(55)
3.50	176(44)	175(57)
4.00	167(46)	164(60)
4.50	154(46)	152(57)
5.00	148(48)	141(60)
6.00	130(52)	124(57)
7.00	119(64)	109(58)
8.00	116(63)	100(55)
10.00	98.1(61)	97.5(61)
12.00	73.2(50)	85.7(48)
16.00	48.3(76)	50.5(64)
24.00	8.10(159)	12.2(157)
30.00	1.01(510)	0.648(510)
$AUC(0\text{-}T)_{ng.hr/ml}$	1925(44)	1985(49)
$AUC(0\text{-}Inf)_{ng.hr/ml}$	2487(34)	2543(44)
$CMAX_{ng/ml}$	231(39)	234(48)

C. M5:

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity), lnCMAX, TMAX, KEL and T1/2. The results are summarized in the tables below:

Table V

M5 Comparative Pharmacokinetic Parameters
Fasting Study; Dose = 400 mg; n = 26

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	5432*	5541*	[0.92;1.03]	0.98
AUC (0-Inf) ng.hr/ml	6374*	6374*	[0.95;1.06]	1.00
CMAX(ng/ml)	645.5*	652.0*	[0.95;1.04]	0.99
TMAX (hrs)	2.35(64)	1.76(40)		
KEL (1/hrs)	0.185(53)	0.186(60)		
T1/2 (hrs)	5.34(71)	5.53(79)		

*Geometric, LS Means

Table VI
Comparative Mean Plasma Levels of M5
Fasting Study; Dose = 400 mg; n = 26
ng/ml(%CV)

Hour	Mylan	Trental[R]
0	0	0
0.25	57.1(76)	67.9(70)
0.50	253(37)	299(36)
0.75	424(29)	467(24)
1.00	535(27)	568(22)
1.50	575(27)	610(26)
2.00	591(33)	615(24)
2.50	546(29)	569(27)
3.00	517(29)	514(25)
3.50	479(32)	475(25)
4.00	442(34)	433(26)
4.50	418(35)	403(28)
5.00	389(34)	364(30)
6.00	368(29)	329(30)
7.00	311(34)	295(36)
8.00	295(32)	255(36)
10.00	262(27)	257(40)
12.00	210(34)	245(46)
16.00	161(66)	159(75)
24.00	33.1(147)	39.1(127)
30.00	1.32(510)	2.74(302)
$AUC(0\text{-}T)_{ng.hr/ml}$	5615(25)	5727(25)
$AUC(0\text{-}Inf)_{ng.hr/ml}$	6519(22)	6455(22)
$CMAX_{ng/ml}$	669(28)	666(22)

Adverse Effects:

There were two mild headache (test and reference treatments) and one moderate headache reactions (reference treatment) reported.

B. Repeat Multiple-Dose, Fasting Bioequivalence Study: (PENT-9330)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Mylan's pentoxifylline tablets, 400 mg, and Hoechst-Roussel's Trental® Tablets, 400 mg, following oral administration of a 400 mg dose every eight hours for thirteen doses.

Study Investigators and Facilities:

The study was conducted at between March 15 and March 30, 1994. The principal investigator were Plasma samples were assayed by under the supervision of , between April 11 and April 26, 1994 for pentoxifylline and 5-hydoxypentoxifylline, and between September 13 and November 23, 1995 for 1-(3-carboxypropyl)-3,7-dimethylxanthine.

Demographics:

Thirty-six normal, healthy, non-smoking male volunteers between 19-45 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 134 - 207 lbs and 63 - 76 in., respectively.

Inclusion criteria:

Subjects especially did not have any history of: cardiac, pulmonary, renal,

hematopoietic, gastrointestinal, or neurological diseases, adverse reactions or allergy to pentoxifylline or any other methylxanthine, drug and/or alcohol abuse, use of psychotropic agents, or cardiac arrhythmias.

Restrictions:

They were free of all medications at least 14 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed within 48 hours of their check-in appointment until their release from confinement in each period. The subjects fasted for 10 hours prior to and 5 hours after each drug administration. The washout duration between the two phases was one week. Duration of confinement was approximately 9 hours pre-dose until after approximately 8-hour blood draw on Day 5 post-dose.

Treatments and Sampling:

The two treatments consisted of 13 x 400 mg doses of either the test product or reference product, taken orally one 400 mg dose with 240 ml of water every eight hours for thirteen doses.

Test Product: Mylan's Pentoxifylline Tablets, 400 mg, lot # 2Z012A (Batch size of units, potency of 97.6%).

Reference product: Hoechst-Roussel's Trental[R] Tablets, 400 mg, lot # 0784983 (Potency of 100.8%).

Blood samples were collected at predose, 48(Day 3), 72(Day 4), 96(Day 5), 96.25, 96.5, 97.0, 97.5, 98.0, 98.5, 99.0, 99.5, 100.0, 100.5, 101.0, 102.0, and 104.0 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -20°C until shipping to the analytical laboratory.

Assay Methodology:

Pages 19 - 23

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and
TRADE SECRET INFO

Pharmacokinetic Results:

Steady-state pharmacokinetic parameters for PENT, M1 and M5 were calculated. CMAX, TMAX and CMIN were determined from the observed plasma concentration-time profile over the sampling interval (Day 5). AUC_{96-104} at steady-state was the sum of the linear trapezoidal estimation of the areas from the time of the 13th dose to 8 hours post 13th dose (96-104 hours). CSS was AUC_{96-104} divided by the dosing interval (8 hours). FLUCT1 and FLUCT2 were the percent fluctuation calculated as the difference between CMAX and CMIN divided by CSS or CMIN, respectively.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as $LNAUC_{96-104}$ and LNCMAX. The 90% confidence intervals for AUC_{96-104}, CMAX, $lnAUC_{96-104}$ and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

An analysis of steady-state attainment was performed using concentration data from the 48, 72 and 96 hour post dose plasma samples. A regression analysis of the data by subject and treatment were performed. The mean parameter estimates for the resultant slopes and intercepts were tested to find if they were different from zero using Students t-test. Also, an ANOVA with terms for treatment was employed to compare for the mean slope differences between treatments.

Results:

All thirty-six enrolled volunteers completed the clinical portion of the study. Data for all 36 subjects were analyzed for PENT and M1. Only 35 subjects were in the M5 data set because Subject # 26 Period 2 samples were misplaced during long term storage and this subject was excluded fromM5 data analysis.

A. PENT:

Regression analysis showed that all subjects were at steady-state for PENT after 12 doses. T-tests showed that the mean slopes for either Test or Reference treatment of PENT were not significantly different from zero. ANOVA showed no difference in slopes between treatments for PENT.

There was no significant difference (alpha=0.05) between treatments for all analyzed parameters except for $AUC_{96\text{-}104}$ (p=0.0267). The results are summarized in the tables below:

Table VII
PENT Comparative Pharmacokinetic Parameters
Multiple-Dose Study: Dose = 13x400 mg; n = 36

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
$AUC_{96\text{-}104}$ ng.hr/ml	535.4*	589.4*	[0.84;0.99]	0.91
CMAX(ng/ml)	143.1*	144.2*	[0.87;1.13]	0.99
CMIN(ng/ml)	30.6(59)	35.0(60)		
TMAX (hrs)	97.2(1.4)	97.3(1.5)		
FLUCT1(%)	185(53)	156(24)		
FLUCT2(%)	510(84)	419(54)		

*Geometric, LS Means

Table VIII
Comparative Mean Plasma Levels of PENT
Multiple-Dose Study: Dose = 13x400 mg; n = 36
ng/ml(CV)

Hour	Trental	Mylan
0	0	0
48	49.0(72)	44.1(79)
72	42.9(163)	30.1(71)
96	57.6(130)	43.7(110)
96.25	88.4(86)	82.5(122)
96.5	146(76)	138(91)
97.0	135(73)	137(87)
97.5	125(64)	108(72)
98.0	108(65)	94.8(63)
98.5	89.7(63)	80.4(55)
99.0	74.5(46)	70.0(48)
99.5	71.0(72)	67.9(69)
100	67.5(83)	62.6(62)
100.5	62.5(61)	52.9(56)
101	53.8(61)	50.9(59)
102	84.8(69)	72.6(51)
104	50.8(66)	46.5(68)
$AUC_{96\text{-}104(ng.hr/ml)}$	669(61)	608(57)
$CMAX_{ng/ml}$	168(68)	171(73)

B. M1:

Regression analysis showed that eleven subjects had slopes significantly different from zero: Subjects 19, 20, 23, 24, 25, 26, 27, 29, 31, 34, and 35; these slopes however had a negative value. T-tests showed that the mean slope for either treatment Test or Reference of M1 was different from zero, but also had a negative value.. ANOVA showed no difference in slopes between treatments for M1.

There was no significant difference (alpha=0.05) between treatments for all analyzed parameters except for LNCMAX (p=0.0361). The results are summarized in the tables below:

Table IX
M1 Comparative Pharmacokinetic Parameters
Multiple-Dose Study; Dose = 13x400 mg; n = 36

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
AUC_{96-104} ng.hr/ml	1574*	1694*	[0.87;0.99]	0.93
CMAX(ng/ml)	310.7*	339.4*	[0.85;0.98]	0.92
CMIN(ng/ml)	115(57)	128(64)		
TMAX (hrs)	84.7(26)	80.9(28)		
FLUCT1(%)	108(30)	111(30)		
FLUCT2(%)	226(45)	239(59)		

*Geometric, LS Means

Table X
Comparative Mean Plasma Levels of M1
Multiple-Dose Study; Dose = 13x400 mg; n = 36
ng/ml(CV)

Hour	Trental	Mylan
0	0	0
48	297(64)	260(65)
72	239(93)	183(62)
96	213(77)	192(71)
96.25	210(78)	190(74)
96.5	272(71)	245(73)
97.0	305(60)	309(70)
97.5	331(57)	332(74)
98.0	318(58)	314(70)
98.5	302(58)	282(66)
99.0	283(57)	260(62)
99.5	269(63)	245(62)
100	251(61)	230(67)
100.5	227(61)	216(68)
101	219(53)	207(69)
102	205(55)	197(72)
104	143(69)	129(62)
$AUC_{96\text{-}104(ng.hr/ml)}$	1940(57)	1837(65)
$CMAX_{ng/ml}$	392(58)	361(67)

C. M5:

Regression analysis showed that six subjects had slopes significantly different from zero: Subjects 19, 23, 24, 32, 33, and 34; these slopes however had a negative value. T-tests showed that the mean slope for either treatment A or B of M1 was different from zero, but also had a negative value.. ANOVA showed no difference in slopes between treatments for M5.

There was no significant difference (alpha=0.05) between treatments for all analyzed parameters except for AUC (p=0.0338), LNAUC (p=0.0215) and LNCMAX (p=0.0460). The results are summarized in the tables below:

Table XI
M5 Comparative Pharmacokinetic Parameters
Multiple-Dose Study: Dose = 13x400 mg; n = 35

Parameters	Mylan Mean (CV)	Trental[R] Mean (CV)	90% C.I.	Ratio T/R
AUC_{96-104} ng.hr/ml	5631*	6016*	[0.89;0.98]	0.93
CMAX(ng/ml)	1138*	1219*	[0.88;0.99]	0.93
CMIN(ng/ml)	383(32)	382(40)		
TMAX (hrs)	92.5(16)	87.6(22)		
FLUCT1(%)	110(27)	115(27)		
FLUCT2(%)	237(60)	272(56)		

*Geometric, LS Means

Table XII
Comparative Mean Plasma Levels of M5
Multiple-Dose Study; Dose = 13x400 mg; n = 35
ng/ml(CV)

Hour	Trental	Mylan
0	0	0
48	810(52)	703(48)
72	726(44)	607(49)
96	748(40)	663(44)
96.25	740(36)	670(43)
96.5	874(31)	859(36)
97.0	1097(22)	1061(29)
97.5	1135(17)	1066(28)
98.0	1030(19)	995(27)
98.5	950(18)	908(26)
99.0	861(20)	799(25)
99.5	810(20)	777(24)
100	762(22)	721(24)
100.5	706(22)	637(22)
101	653(21)	597(23)
102	617(35)	565(26)
104	420(50)	398(33)
$AUC_{96-104(ng.hr/ml)}$	6117(20)	5749(22)
$CMAX_{ng/ml}$	1243(20)	1177(28)

Adverse Effects:

There were five mild headache reactions reported during both test and reference treatments for Subjects 9 and 36, and during test treatment for Subject 25.

IV. Firm's Response to Deficiency Comments Concerning Single-Dose Food Study (PENT-9327):

"Subject 5 was originally assayed on Curve BK011. Subject 5 was then re-extracted with Curve BK022 because the 5-hydroxypentoxifylline portion of Standard Curve BK011 was rejected due to contamination. Since the assay is for both pentoxifylline and 5-hydroxypentoxifylline, subject 5 pentoxifylline is listed as assayed with both curves. However, subject 5 pentoxifylline values are from the original assay generated from Curve BK011, except for sample 5, 1, 2, a suspected pharmacokinetic outlier; which was calculated from the reassay Curve BK022." (The median pentoxifylline value of sample 5, 1, 2 was reported as final value.)

V. Dissolution Testing:

Drug (Generic Name): Pentoxifylline
Firm: Mylan Pharmaceuticals
Dose Strength: 400 mg
ANDA # 74-425
Submission Date: April 17, 1996

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket __ Paddle X RPM 50 or 75 Units Tested: 12
Medium: Aqueous buffer of pH 1.5, 4.5, 6.5 or 7.5 Volume: 900 ml
Reference Drug: (Manuf.) Trental[R] (Hoechst-Roussel)
Assay Methodology: Not given

II. Results of In-Vitro Dissolution Testing:

Paddle Speed 50 rpm, pH 1.5

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	19		(2.2%)	20		(3.0%)
8	49		(4.1%)	52		(3.2%)
12	66		(2.0%)	69		(3.1%)
24	97		(2.6%)	101		(2.4%)

Paddle Speed 50 rpm, pH 4.5

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	18		(4.5%)	20		(5.5%)
8	47		(2.2%)	50		(2.9%)
12	61		(2.0%)	66		(2.3%)
24	94		(3.0%)	100		(1.5%)

Paddle Speed 50 rpm, pH 6.5

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	17	_	(2.7%)	19		(2.6%)
8	44	_	(2.8%)	49		(2.1%)
12	59	_	(2.7%)	66		(2.2%)
24	92	_	(2.2%)	99		(1.8%)

Paddle Speed 50 rpm, pH 7.5

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	17	_	(2.3%)	19		(1.3%)
8	44	_	(1.3%)	48		(1.9%)
12	60	_	(2.6%)	64		(2.1%)
24	91	_	(2.7%)	96		(1.8%)

Paddle Speed 75 rpm, pH 1.5: (Proposed conditions)

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	20		(2.8%)	21		(2.3%)
8	53		(2.5%)	53		(3.2%)
12	70		(2.9%)	73		(3.4%)
24	96		(1.4%)	104		(2.4%)

Paddle Speed 75 rpm, pH 4.5

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	20		(7.4%)	22		(5.8%)
8	51		(6.5%)	53		(3.5%)
12	72		(6.3%)	71		(3.3%)
24	97		(2.3%)	105		(4.1%)

Paddle Speed 75 rpm, pH 6.5

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	19		(7.6%)	20		(6.3%)
8	52		(8.2%)	51		(4.1%)
12	68		(6.9%)	98		(3.9%)
24	96		(1.5%)	102		(2.3%)

Paddle Speed 75 rpm, pH 7.5

Sampling Times (Hrs.)	Test Product Lot # 2C003B Strength (mg) 400			Reference Product Lot # 0782965 Strength (mg) 400		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
2	19	_	(4.9%)	19	-	(7.8%)
8	48	_	(2.1%)	50	-	(2.9%)
12	64	_	(2.1%)	67	-	(3.0%)
24	93	_	(2.8%)	102		(1.9%)

III. Proposed Specifications:

Based on the results of the pH profiles, Mylan proposes the following dissolution testing procedure testing and specifications for its product:

Apparatus: 2(paddles) at 75 rpm
Medium: SGF (pH 1.5); Volume : 900 ml
Tolerances:

Sampling Schedule	Limits
2 hours	
8 hours	
12 hours	
24 hours	

VI. Deficiencies:

1. In the Repeat Single-Dose Fasting Study, there were many subjects without AUC(0-Inf) calculated for each analyte, and several subjects with only 2 points used for calculating the terminal slope. The firm should provide the SOP for the individual elimination rate constant determination.

3. The firm should submit a long-term stability study covering the actual sample storage duration of 618 days for the metabolite M5 of the repeat multiple-dose study (PENT-9330). The study is considered incomplete until the long-term stability data are found acceptable.

4. Since the Repeat Multiple-Dose study and the Food study were conducted on the original formulation with and the Repeat Fasting Single-Dose study and the in-vitro dissolution testing were conducted on the formulation, there is lack of in-vivo or in-vitro testing data comparing the original formulations with the new formulation for demonstrating that the removal of the does not affect the bioavailability of the reformulated product. **Since the is only used for tablet appearance and to enhance the speed of the bottle filling, in-vitro dissolution data comparing the two formulations are considered sufficient bioequivalence requirement for the reformulated product in addition to the Fasting Single-Dose Study already submitted.**

The firm should be advised to conduct the dissolution testing on the biolot of the formulation and a lot of the original formulation, using the FDA-recommended dissolution procedure and specifications.

5. The in-vitro dissolution testing conducted by Mylan Pharmaceuticals on its Pentoxifylline ER Tablets, 400 mg, has been found acceptable.

However, the Division of Bioequivalence recommends that the firm-proposed procedure and specifications be modified as follows:

(i) The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of SGF without enzyme at 37°C using USP XXIII apparatus II(paddle) at **50 rpm**. Since the results between the paddle speed of 50 rpm and 75 rpm (with other dissolution conditions being equal) are essentially equivalent, the lower paddle speed is preferred by the division.

(ii) The tentative specifications for the test product should be: (Derived from the rule that the range should be approximately ±10% of the label claim of the mean)

Sampling Schedule	Limits
2 hours	
8 hours	
12 hours	
24 hours	

VII. Comments:

N Thomson 4/28/97

1. The food study previously submitted and reviewed (See summary of the study results in this review attachment) comparing Mylan's Pentoxifylline ER 400 mg Tablets, lot # 2Z012A, with Hoechst-Roussel's Trental 400 mg tablet, lot # 0787652, demonstrates that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) of PENT and M1, under non-fasting conditions.

NOTE: According to the Deficiency letter issued October 17, 1994 by the Division of Bioequivalence, M5 plasma concentrations of the food study were not asked for reassay. The firm had submitted this study prior to the issuance of the Guidance of Pentoxifylline ER Tablets In Vivo Bioequivalence and In Vitro Dissolution Testing (December 22, 1995).

2. In the Repeat Single-Dose Fasting Study (Protocol No. PENT-9607), there were two subjects with the highest peak being the first non-zero PENT concentration: Subjects #9 (Treatment A) and 11 (Treatment B). DBE's current practice requires excluding these subjects from the statistical analysis. The reviewer re-analyzed the data for PENT, M1 and M5 without Subjects #9 and 11. The 90% confidence intervals for log-transformed CMAX, AUC(0-T) and AUC(0-Infinity) of the above analytes are as follows:

	LnCMAX	LnAUC(0-T)	LnAUC(0-Inf)
PENT	[0.81;1.08] $_{n=24}$	[0.87;1.10] $_{n=24}$	[0.79;1.22] $_{n=17}$
M1	[0.88;1.11] $_{n=24}$	[0.86;1.06] $_{n=24}$	[0.90;1.11] $_{n=19}$
M5	[0.93;1.04] $_{n=24}$	[0.92;1.04] $_{n=24}$	[0.94;1.06] $_{n=18}$

The 90% confidence interval for log-transformed AUC(0-Inf) of PENT, without Subjects Nos. 9 and 11, is outside the limit of [0.80;1.25]. However, AUC(0-Inf) calculation only included 17 subjects, and was not considered as accurate assessment of the extent of absorption as AUC(0-T), of which the 90% confidence interval was within the limit of [0.80;1.25]. The 90% confidence interval of log-transformed CMAX values was also within the acceptable limit.

VIII. Recommendations:

1. The repeat multiple-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Pentoxifylline ER Tablets, 400 mg, lot # 2Z012A, comparing it with the reference product, Trental^R Tablets, 400 mg, lot # 0784983, has been found incomplete by the Division of Bioequivalence due to the reasons cited in the Deficiencies Nos. 2 and 3 above.

2. The repeat single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Pentoxifylline ER Tablets, 400 mg, lot # 2C003B, comparing it with the reference product, Trental^R Tablets, 400 mg, lot # 0782965, has been found incomplete by the Division of Bioequivalence due to the reasons cited in the Deficiency No. 1 above.

3. The non-fasting single-dose bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Pentoxifylline ER Tablets, 400 mg, lot # 2Z012A, comparing it with the reference product, Trental^R Tablets, 400 mg, lot # 0787652 has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Pentoxifylline ER Tablets, 400 mg, manufactured by Mylan Pharmaceuticals is bioequivalent to the reference product, Trental Tablets, 400 mg, manufactured by Hoechst-Roussel under non-fasting conditions.

4. The in-vitro dissolution testing conducted by Mylan Pharmaceuticals on its Pentoxifylline ER Tablets, 400 mg, has been found acceptable.

However, the Division of Bioequivalence recommends that the firm-proposed

procedure and specifications be modified as follows:

(i) The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of SGF without enzyme at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. Since the results between the paddle speed of 50 rpm and 75 rpm (with other dissolution conditions being equal) are essentially equivalent, the lower paddle speed is preferred by the division.

(ii) The tentative specifications for the test product should be: (Derived from the rule that the range should be approximately ±10% of the label claim of the mean, for more closely reflecting the actual observed data submitted)

Sampling Schedule	Limits
2 hours	
8 hours	
12 hours	
24 hours	

The firm should be informed of the Recommendations and all Deficiencies (including Deficiency No. 6).

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG _____ 4/22/97

Concur: _____ _____ Date: 4/25/97
Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

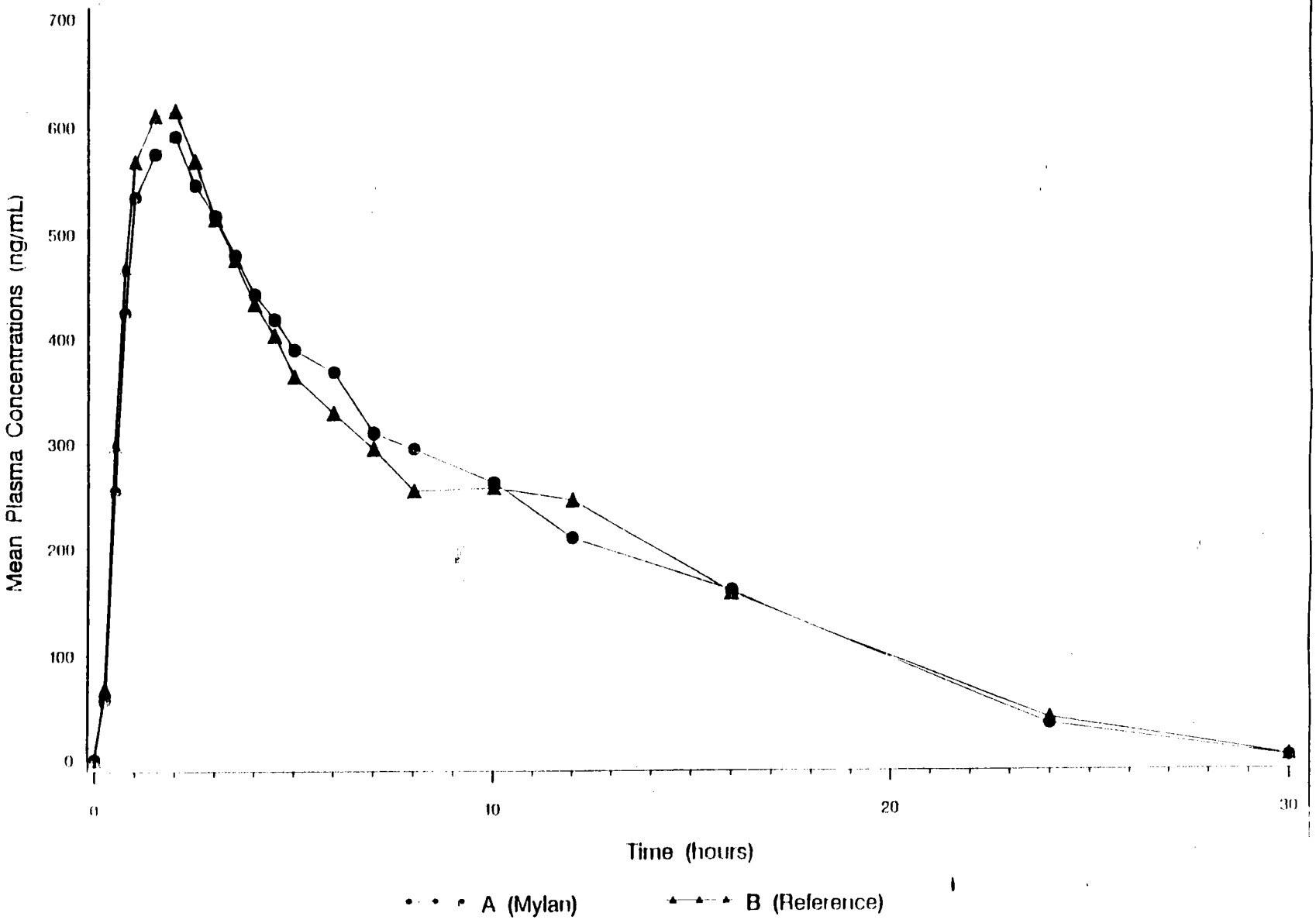
cc: ANDA # 74-425 (original, duplicate), HFD-052(Huang, Nguyen), Drug File, Division File

Hnguyen/02-26-97/WP #74425sd.o96/Revised 04-01-97, 04-07-97, 04-22-97
Attachments: 15 pages

PENTOXIFYLLINE (PENT – 9607)

Total Dose: 400 mg (1x400mg Tablet), Study Type: Fasting

Mean 1 – (3 – Carboxypropyl) Plasma Concentrations

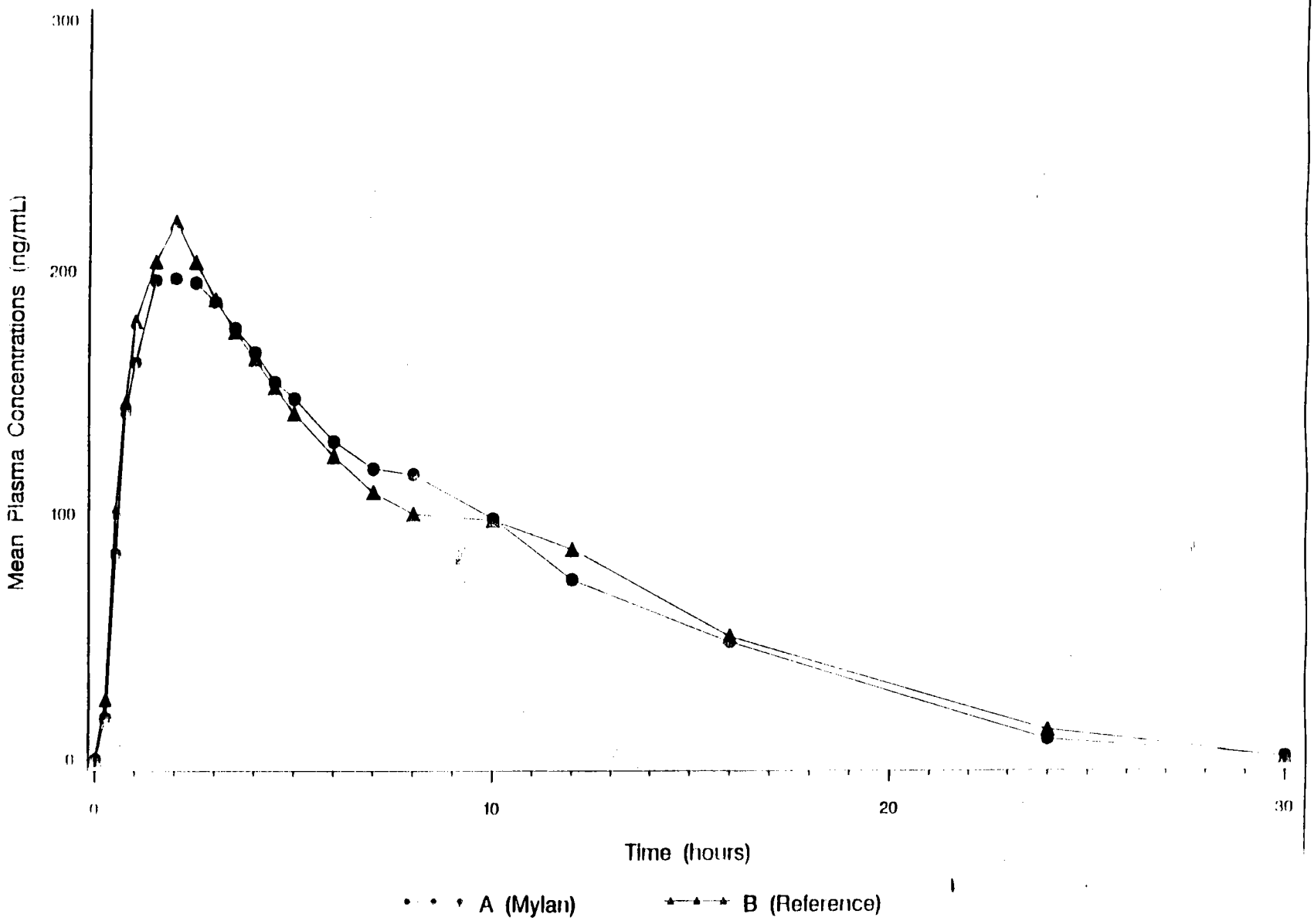


NP # 74425sd.096 Attachment 1 of 15

PENTOXIFYLLINE (PENT – 9607)

Total Dose: 400 mg (1x400mg Tablet), Study Type: Fasting

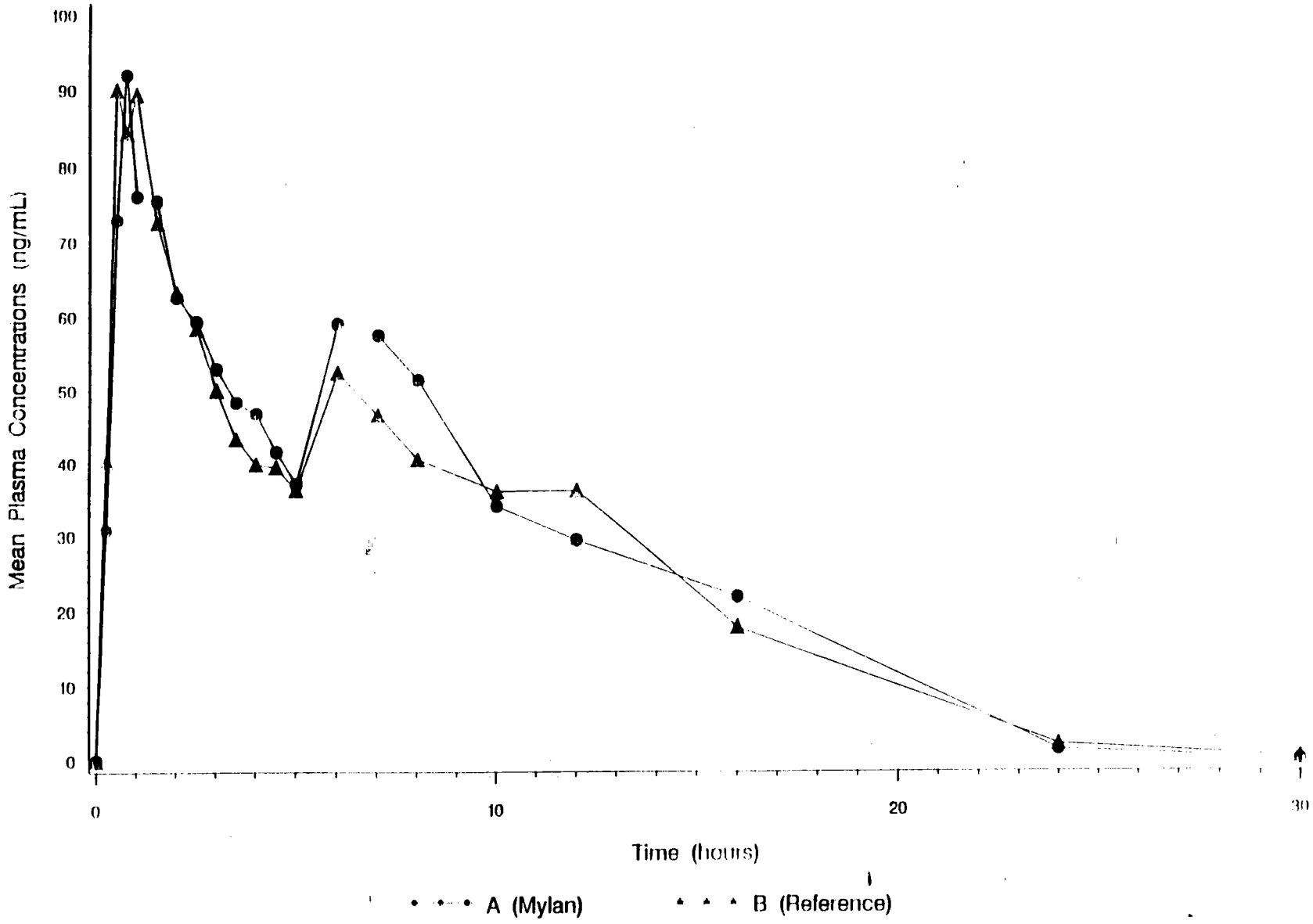
Mean 5 – Hydroxypentoxifylline Plasma Concentrations



PENTOXIFYLLINE (PENT – 9607)

Total Dose: 400 mg (1x400mg Tablet), Study Type: Fasting

Mean Pentoxifylline Plasma Concentrations

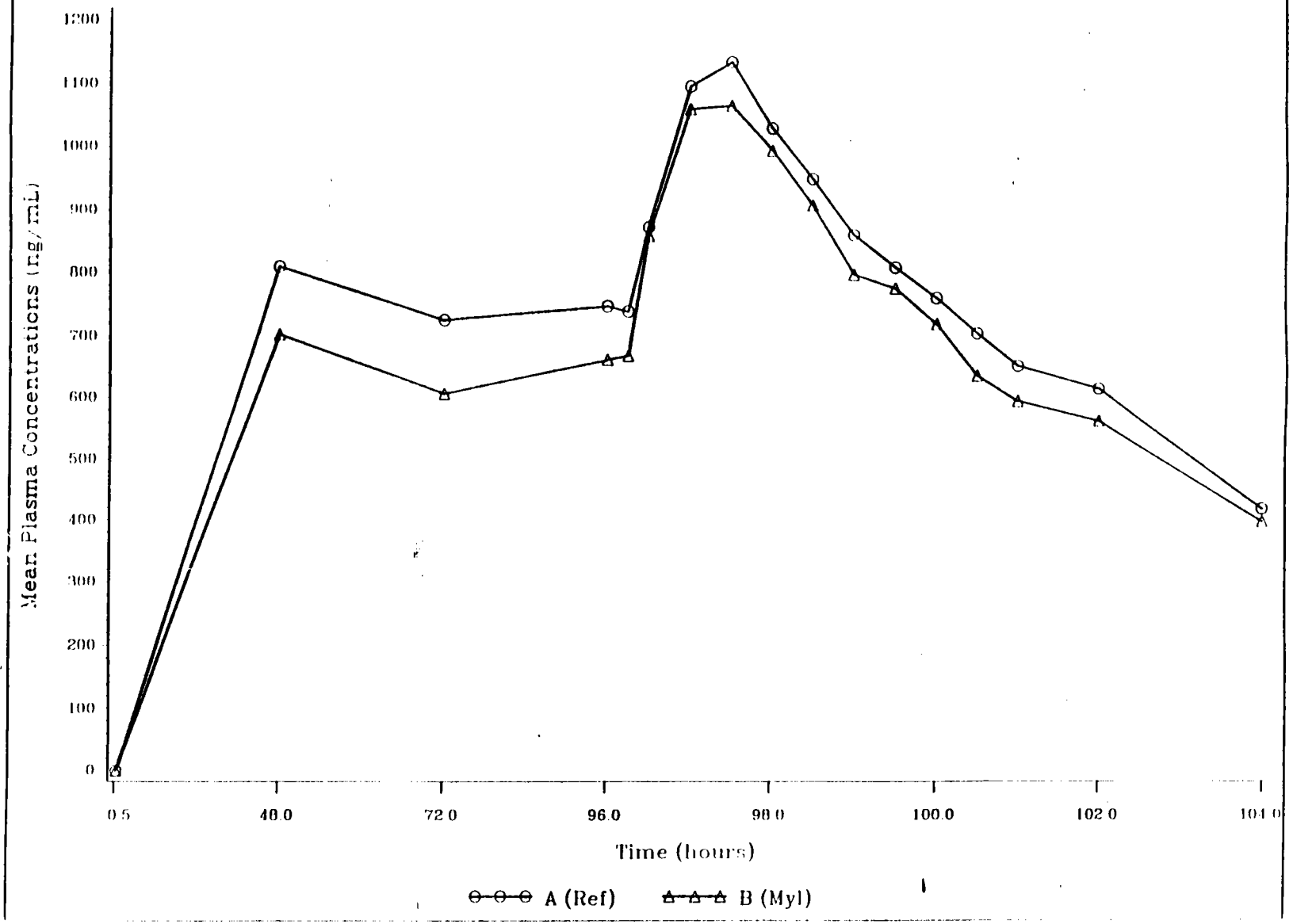


74425 Sd 096 Attachment 3 of 15

PENTOXIFYLLINE (PENT–9330)

Total Dose: 1 x 400 mg (400 mg) Tablet, Study Type: Steady State

Mean Carboxypropyl Dimethylxanthine Plasma Concentrations



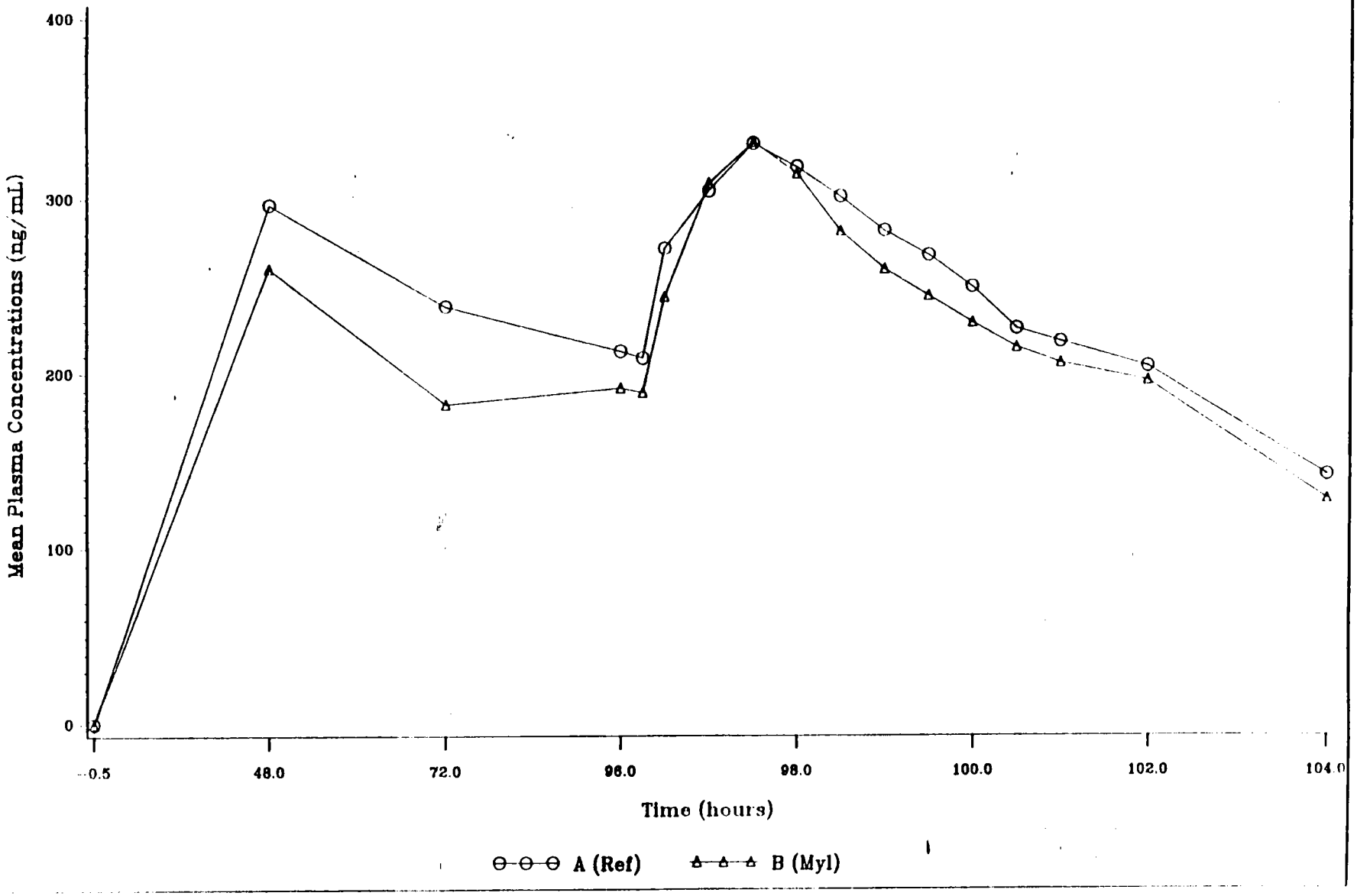
NP # 74,255 096 Attachment #15

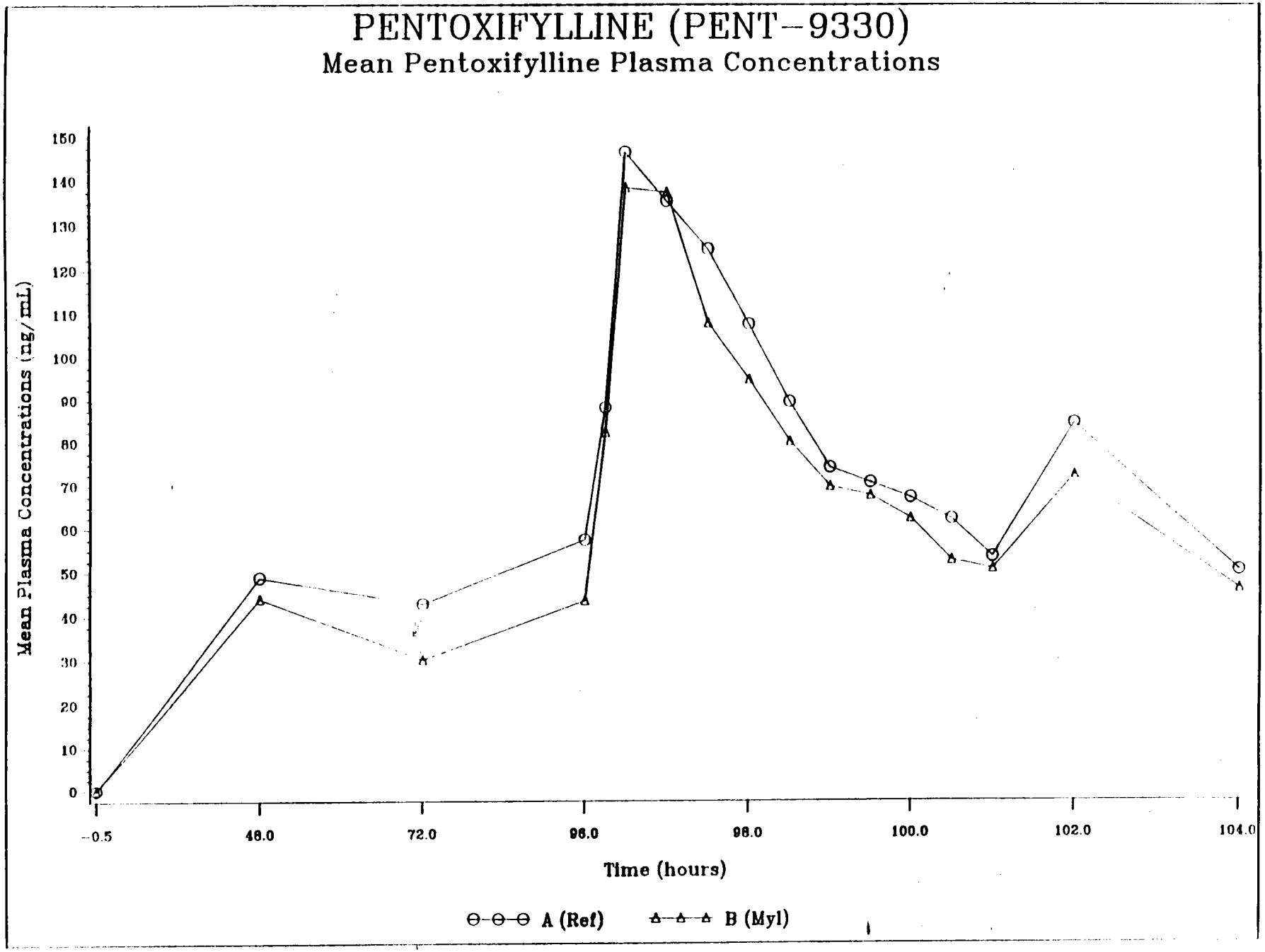
NP # 74425 sd.096 Attachment 5 of 15

1737

PENTOXIFYLLINE (PENT-9330)

Mean 5-Hydroxypentoxifylline Plasma Concentrations





74425sd 096 Attachment 6 of

WP # 74425sd.096
Attachment 7 of 15

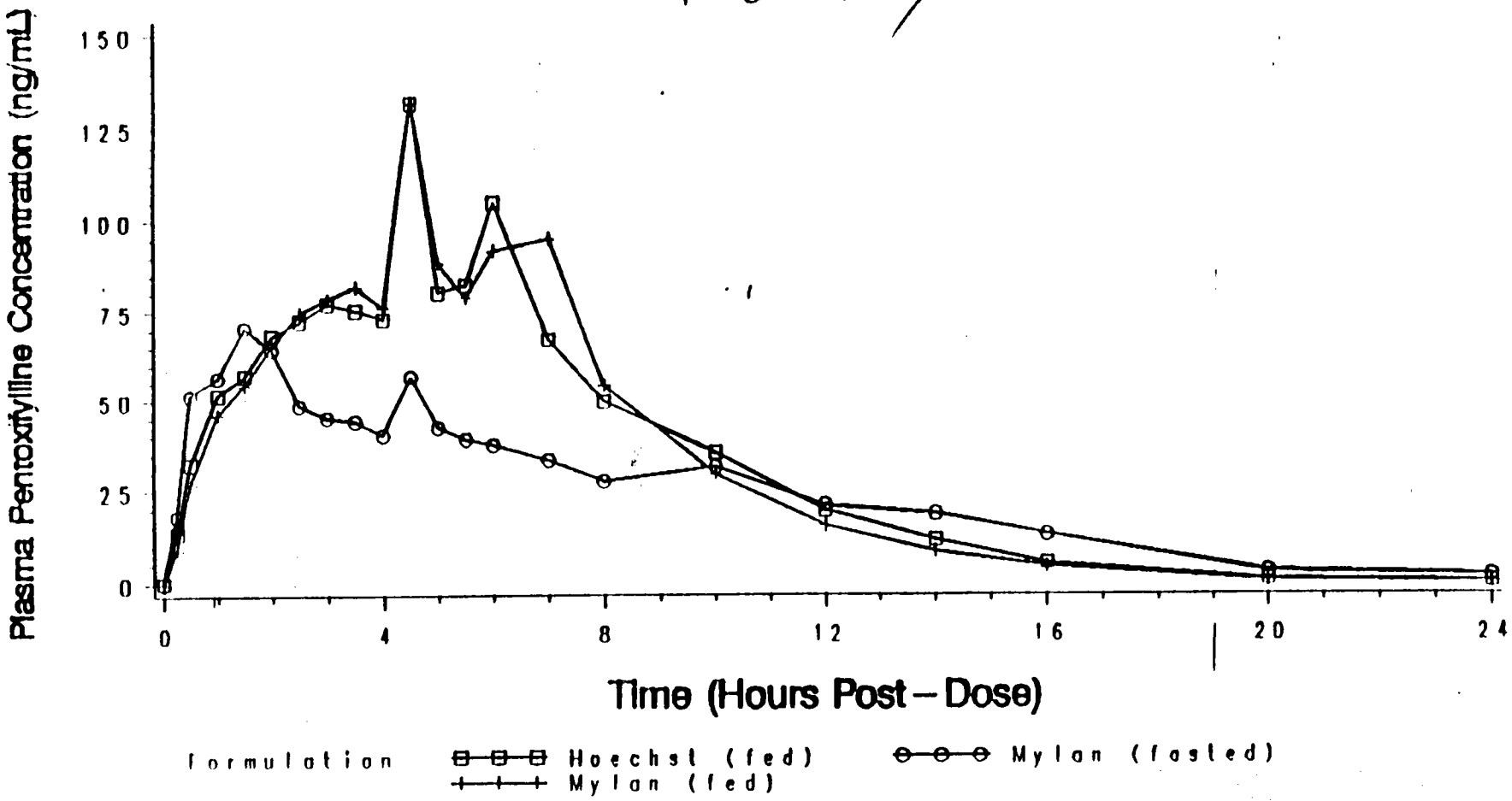
Figure 2

Project No. 930038

Mean Human Plasma Pentoxifylline Concentrations

(Linear Plot)

Food Study



WP# 74425sd.096
Attachment 3 of 15

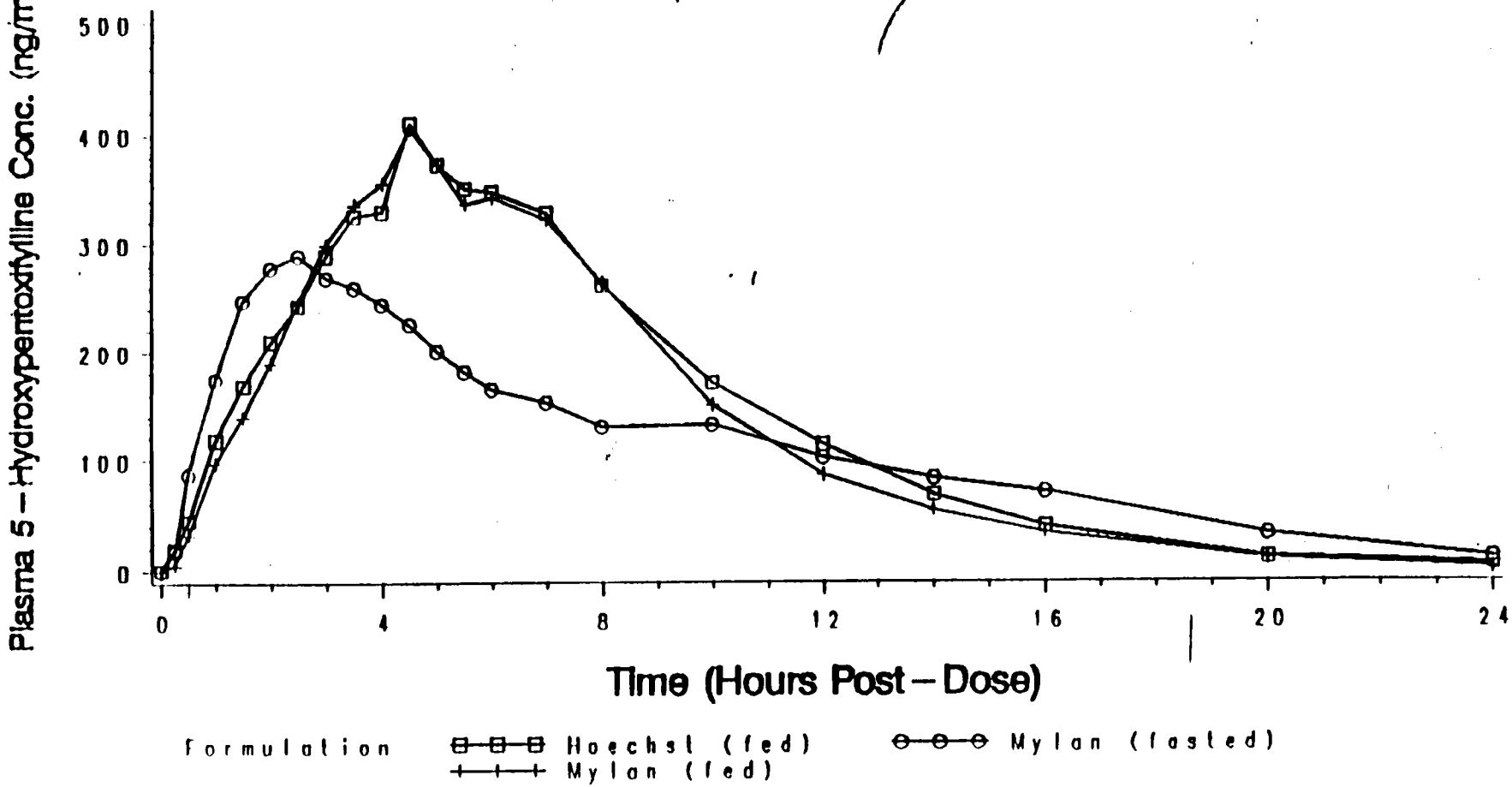
Figure 4

Project No. 930038

Mean Human Plasma 5-Hydroxypentoxifylline Concentrations

(Linear Plot)

Food Study



NP# 74-25-24-096 Attachment 9 of 15

DISSOLUTION PROFILE

PRODUCT: Pentoxifylline Tablets
LOT NO.: 2C003B
DOSAGE: 400 mg

PROCEDURE: PENT-FP-DISS-~~1~~ 2 4/17/96 [illegible]

CONDITION: Dissolution Medium: Simulated Gastric Fluid (no enzyme) @ 37° ± 0.5°C, 900 mL
Apparatus: 2 (paddle) @ 50 rpm
Sample Times @ 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, & 24 hour

	TIME POINT											
Tablet No.	1 Hrs	2 Hrs	4 Hrs	6 Hrs	8 Hrs	10 Hrs	12 Hrs	14 Hrs	16 Hrs	18 Hrs	20 Hrs	24 Hrs
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
AVERAGE	13%	19%	31%	41%	49%	58%	66%	73%	79%	84%	91%	97%
RSD	2.2%	3.1%	2.7%	2.2%	4.1%	2.4%	2.0%	2.6%	3.2%	2.3%	2.2%	2.6%
MI												
M												

DISSOLUTION PROFILE

PRODUCT: Trental® Tablets
LOT NO.: 0782965
DOSAGE: 400 mg

PROCEDURE: PENT-FP-DISS-~~1~~2 [illegible] 4/17/96

CONDITION: Dissolution Medium: Simulated Gastric Fluid (no enzyme) @ 37° ± 0.5°C, 900 mL
Apparatus: 2 (paddle) @ 75 rpm
Sample Times @ 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, & 24 hour

	TIME POINT											
Tablet No.	1 Hrs	2 Hrs	4 Hrs	6 Hrs	8 Hrs	10 Hrs	12 Hrs	14 Hrs	16 Hrs	18 Hrs	20 Hrs	24 Hrs
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
AVERAGE	14%	21%	34%	45%	53%	63%	73%	81%	88%	94%	100%	104%
RSD	2.9%	2.3%	2.7%	3.4%	3.2%	2.9%	3.4%	3.4%	3.8%	3.7%	5.8%	2.4%
MIN												
MAX												

DP# 1025 sd. 096 Attachment 11 of 15

Table 7 - Mean Reported Plasma Concentrations of Pentoxifylline (Food Study, N = 15)

Time (hr)	Trt. A mean, ng/ml	(test, fasted) CV (%)	Trt. B mean, ng/ml	(test, fed) CV (%)	Trt. C mean, ng/ml	(ref., fed) CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
0	0.00	-	0.00	-	0.00	-	-	-
0.25	18.089	93.2	9.154	143	13.496	188	-32.17	-49.39
0.5	51.343	50.8	26.863	106	32.413	103	-17.12	-47.68
1	56.553	49.8	46.107	83.7	51.725	72.3	-10.86	-18.47
1.5	70.497	67.9	54.445	59.5	57.069	49.6	-4.60	-22.77
2	64.443	73.3	65.361	53.1	68.322	73.5	-4.33	1.42
2.5	48.547	70.7	74.649	52.9	72.245	61	3.33	53.77
3	45.198	66.9	78.45	52.5	77.32	66.8	1.46	73.57
3.5	44.251	63.5	81.86	54	75.379	58.5	8.60	84.99
4	40.497	68.3	76.264	63.5	72.983	64.5	4.50	88.32
4.5	56.705	75.8	131.83	70.3	131.84	88.5	-0.01	132.48
5	42.556	59.6	88.391	66.2	80.325	85.1	10.04	107.71
5.5	39.317	61.1	78.98	90.5	82.481	111	-4.24	100.88
6	37.643	50.6	91.895	154	104.98	134	-12.46	144.12
7	33.515	50.8	95.184	144	67.309	137	41.41	184.00
8	27.589	65.8	54.301	130	49.897	102	8.83	96.82
10	31.594	56.5	29.541	97.2	35.459	121	-16.69	-6.50
12	21.066	65.9	15.394	85.6	19.6	85[1]	-21.50	-26.92
14	18.676	73.9	8.328	111	11.557	97.4	-27.94	-55.41
16	13.007	91.4	4.112	138	5.219	167	-21.21	-68.39
20	2.816	229	0.333	387	0.578	387	-42.39	-88.17
24	1.705	229	0.00	-	0.00	-	-	-

[1] N = 14

Trt. A = pentoxifylline (Mylan, fasting), 1 X 400 mg
Trt. B = pentoxifylline (Mylan, fed), 1 X 400 m
Trt. C = Trental (Hoechst, fed), 1 X 400 mg

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Table 8 - Mean Reported Plasma Concentrations of M1 (Food Study, N = 15)

Time (hr)	Trt. A mean, ng/ml	CV (%)	Trt. B mean, ng/ml	CV (%)	Trt. C mean, ng/ml	CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
0	0.00	-	0.00	-	0.00	-	-	-
0.25	17.35	118	5.01	185	19.29	260	-74.03	-71.12
0.5	86.41	62	32.48	113	44.62	126	-27.21	-62.41
1	174.1	40	96.91	82	118.28	74	-18.07	-44.35
1.5	247.4	35	139.44	66	168.65	54	-17.32	-43.64
2	277.7	48	189.73	59	209.52	48	-9.45	-31.69
2.5	289.1	51	245.17	63	242.76	47	0.99	-15.18
3	268.7	52	299.6	58	289.03	49	3.66	11.50
3.5	259.4	52	335.37	52	325.43	45	3.05	29.27
4	244.2	51	355.73	49	329.69	49	7.90	45.70
4.5	225.6	57	404.07	48	410.41	55	-1.54	79.09
5	201.0	49	373.25	50	372.99	68	0.07	85.72
5.5	181.6	50	336.4	56	351.25	76	-4.23	85.28
6	165.5	46	342.51	71	348.08	83	-1.60	106.94
7	153.2	44	322.36	90	328.47	100	-1.86	110.42
8	130.7	39	264.54	102	262.11	98	0.93	102.42
10	132.4	52	151.09	78	171.73	78	-12.02	14.15
12	102.5	47	86.13	70	114.59	79	-24.84	-15.96
14	83.31	53	53.86	89	68.18	87	-21.00	-35.35
16	70.46	77	33.7	94	39.39	112	-14.45	-52.17
20	32.35	131	9.65	125	10.55	171	-8.53	-70.17
24	11.16	148	0.7	387	4.45	180	-84.27	-93.73

Trt. A = pentoxifylline (Mylan, fasting), 1 X 400 mg
Trt. B = pentoxifylline (Mylan, fed), 1 X 400 mg
Trt. C = Trental (Hoechst, fed), 1 X 400 mg

Table 9 - Mean Reported Pharmacokinetic Parameters of Pentoxifylline (Food Study, N = 15, Arithmetic Means)

Parameter	Trt. A (mean)	CV (%)	Trt. B (mean)	CV (%)	Trt. C (mean)	CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
AUC(0-t)	559.5	60	751.7	73	755.6	75	-0.52	34.35
AUCINF	749.3	60[1]	915.2	76[2]	940	75[2]	-2.64	22.14
CMAX	88.85	55	170.21	74	161.92	79	5.12	91.57
TMAX (hr)	1.737	86	4.767	44	4.617	47	3.25	174.44
KEL (hr^{-1})	0.1841	22[1]	0.2635	48[2]	0.4138	62[2]	-36.32	43.13
T (hr)	3.927	23[1]	3.077	38[2]	2.223	51[2]	38.42	-21.65

NDA 74 625 sd. 096 Attachment 13 of 15

Table 10 - Mean Reported Pharmacokinetic Parameters of M1 (Food Study, N = 15, Arithmetic Means)

Parameter	Trt. A (mean)	CV (%)	Trt. B (mean)	CV (%)	Trt. C (mean)	CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
AUC(0-t)	2675.3	49	3066	53	3259.5	55	-5.94	14.60
AUCINF	2447.2	45[3]	3185.1	52[4]	3965.3	47[3]	-19.68	30.15
CMAX	307.66	48	505.85	51	499.75	55	1.22	64.42
TMAX (hr)	2.333	24	5.47	36	5.139	41	6.44	134.46
KEL (hr^{-1})	0.2115	31[3]	0.3436	60[4]	0.4512	33[3]	-23.85	62.46
T (hr)	3.673	41[3]	2.869	65[4]	1.697	33[3]	69.06	-21.89

Tables 9 & 10: [1] N = 7 [2] N = 8 [3] N = 10 [4] N = 14

Table 11 - Least Squares Means and Ratios for Pentoxifylline and M1 as Reported (Food Study, N = 15)

Drug	Parameter	Trt. A	Trt. B	Trt. C	Ratio[1]
Pent.	AUC(0-t)	560.2	715.9	790.7	90.5
	logAUC(0-t)	-	-	-	98.1
	CMAX	89.775	160.55	170.64	94.1
	logCMAX	-	-	-	107.8
M1	AUC(0-t)	2663.7	2989.1	3348	89.3
	logAUC(0-t)	-	-	-	93.6
	CMAX	316.2	485.33	511.72	94.8
	logCMAX	-	-	-	103.1

[1] untransformed: ratio (as %) = Trt. B_{LSM} / Trt. C_{LSM}; log-transformed: ratio (as %) of geometric means = exp(logB - logC), where (logB - logC) is the estimate from the ANOVA

units for AUC's: ng*hr/ml; units for CMAX: ng/ml

Trt. A = pentoxifylline (Mylan, fasting), 1 X 400 mg
Trt. B = pentoxifylline (Mylan, fed), 1 X 400 mg
Trt. C = Trental (Hoechst, fed), 1 X 400 mg

Table 12 - Ratios of Least Squares Geometric Means as Determined by the Reviewer (Food Study, N = 15)

Analyte	Condition	Ratio - AUC(0-t)	Ratio - CMAX
Pent.	1	1.005	1.076
	2	0.981	1.078
	3	1.002	1.084
M1	1	0.959	1.02
	2	0.936	1.031
	3	0.947	1.016

Condition:
1 Standard model, all three treatments included
2 Residual model, all three treatments included
3 Standard model, only Treatments B and C included

QUANTITATIVE COMPOSITION

PENTOXIFYLLINE EXTENDED-RELEASE TABLETS, 400 MG

ACTIVE COMPONENT	MG PER TABLET
Pentoxifylline	400.0
INACTIVE COMPONENTS (CORE)	
Povidone, USP	
Purified Water, USP	
Hydroxyethylcellulose, NF	
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
TOTAL	575.0
INACTIVE COMPONENTS FILM-COAT	
(Lavender	
Purified Water, USP	
AVERAGE TARGET FILM COAT WEIGHT	
RANGE	

[1] Purified Water, USP is added to the product as a processing aid but does not contribute to the total weight, therefore, Purified Water, USP quantities are expressed parenthetically.

Original

QUANTITATIVE COMPOSITION

PENTOXIFYLLINE TABLETS 400 MG

	MG PER TABLET
ACTIVE COMPONENT	
Pentoxifylline	400.0
INACTIVE COMPONENTS (CORE)	
Povidone, USP (Plasdone K-90)	
Purified Water, USP	
Hydroxyethylcellulose, NF	
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
TOTAL	575.0
INACTIVE COMPONENTS FILM-COAT	
(Lavender	
Purified Water, USP	
AVERAGE TARGET FILM COAT WEIGHT	
RANGE	

Purified Water, USP is added to the product as a processing aid but does not contribute to the total weight, therefore, Purified Water, USP quantities are expressed parenthetically.

3356

3357

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DIV

AUG 13 1994

Pentoxifylline
400 mg extended-release tablet
ANDA #74-425
Reviewer: James D. Henderson
File: 74425S.N93

Mylan Pharmaceuticals
Morgantown, West Virginia
Submitted:
November 19, 1993

REVIEW OF THREE BIOEQUIVALENCE STUDIES

The sponsor has submitted the results of three bioequivalence studies comparing its test product pentoxifylline 400 mg extended-release tablet with the FDA-designated reference product Trental® 400 mg CR tablets (Hoechst Roussel, NDA #18-631, 8/30/84; NCE exclusivity, 8/30/94): 1) single dose fasting study; 2) single dose food study; 3) multiple dose steady-state study. No dissolution data was submitted.

I. SINGLE DOSE FASTING STUDY

A. Study Sites

Clinical Site:

Principal Investigat
Co-Investigator:
Protocol: Bioequivalence Pilot Study of Pentoxifylline Tablets in Healthy Volunteers (4/26/93; IRB approval 5/5/93)
Study #: PENT-9236
Study Dates: Period 1 dosing, 5/18/93; Period 2 dosing 5/25/93
Analytical Site:

Analytical Director:
Analysis Dates: 6/4-21/93

B. Study Design

This was a randomized, single dose, two-way crossover design comparing the test product pentoxifylline 400 mg extended-release tablets with the reference product Trental® 400 mg CR tablets in 13 healthy male volunteers under fasting conditions with a one week washout between treatments. Plasma was analyzed for the parent drug pentoxifylline (P) and the metabolite 5-hydroxypentoxifylline (M1).

C. Subject Selection

Fifteen subjects (14 subjects and one standby) were selected for this study after signing informed consent according to the following criteria:

1. Inclusion Criteria

- males, 19-45 years old
- within ± 10% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983)
- good health as determined by interview, physical examination, hematology, serum chemistry, ECG, and urinalysis
- laboratory values not to exceed 10% of normal limits (with the exception of parameters that are not clinically relevant)

2. Exclusion Criteria

- history or presence of alcohol or drug of abuse, use of psychotropic agents, cardiac arrhythmias, adverse reactions or allergy to any methylxanthine
- presence of significant systemic or organ disease, or acute illness or surgery in the four weeks prior to study start
- exposure to an investigational drug in the four weeks prior to study start
- use of tobacco products
- use of any medication within two weeks of study start
- BP < 90/60 after a five minute rest
- ingestion of alcohol or xanthine-containing beverages within 48 hours of study start

D. Study Procedures

Treatments: After fasting ten hours prior to drug administration, subjects received one of the following treatments:

1) Treatment A (ref.), Trental® 400 mg CR tablet, 1 X 400 mg, Hoechst Roussel Lot #0787652, exp 5/95; potency not stated

2) Treatment B (test), pentoxifylline 400 mg extended-release tablet, 1 X 400 mg, Mylan Lot #2Z012A; manufacturing dates, theoretical batch size, finished batch size, and potency not stated

Each dose was administered with 240 ml of water. After a one week washout, each subject received the alternative treatment.

(Note: In the protocol, p. 172 and 377, Trental® is identified incorrectly as the "Experimental Drug" and pentoxifylline is identified incorrectly as the "Reference Drug".)

Restrictions: Subjects were ambulatory during the study, but strenuous exercise was not permitted and they were not allowed to lie flat for 12 hours. Subjects were confined to the clinical site for at least 24 hours postdose.

Meals and Fluids: Fluids were not allowed for one hour before or after dosing (except for the 240 ml of water given with the dose). Fasting occurred for ten hours prior to dosing, and standardized meals began five hours postdose.

Blood Sampling: Blood samples (10 ml, EDTA Vacutainer) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours postdose. After centrifugation at 4°, plasma was separated and frozen at ≤ -20°.

Monitoring: Blood pressure and pulse rates were measured hourly for the first 8 hours and at 10, 12, and 24 hours.

E. Analytical Methodology and Data Analysis

F. Results

1. Product Information

1. The test product formulation is shown in Table 1 (attached).

2. Clinical

1. **Completion:** Fifteen subjects were enrolled. Subjects 13 and 14 did not report for dosing in Phase I. The standby replaced

Subject 13. Thirteen subjects completed both phases of the study.

2. **Protocol Deviations:** Subjects entered the study in accordance with the criteria noted in the protocol. All blood samples were collected within 2 minutes of the scheduled time for the first 12 hours. All blood samples in excess of 12 hours were drawn within 10 minutes of the scheduled time.

3. **Adverse Events:** None

(Note: Case Report Forms for Study #1 are found in v. 1.7)

3. Pharmacokinetics/Statistics

1. Tables 2 and 3 show the mean plasma concentration vs. time profiles for pentoxifylline and M1, respectively. There were no nonzero predose concentrations for either analyte. For pentoxifylline, there were seven cases where the first nonzero concentration (all at the first sampling time of 0.5 hr) was the CMAX: Trt. A, Subjects 8, 11, 12; Trt. B, Subjects 4, 7, 8, and 12. For M1, there was one case where the first nonzero concentration (at the first sampling time of 0.5 hr) was the CMAX: Trt. A, Subject 11.

2. Tables 4 and 5 show the mean pharmacokinetic parameters for pentoxifylline and M1, respectively. There were no statistically significant sequence ($p > 0.1$), period ($p > 0.05$), or treatment ($p > 0.05$) effects for AUC(0-t), CMAX, or their log-transformed values for either pentoxifylline or M1. Using the GLM procedure of SAS and the original data supplied on diskette, the reviewer confirmed the 90% CI calculations for log-transformed AUC(0-t) and CMAX for both pentoxifylline and M1.

3. Due to the apparent ongoing absorption from the CR product, KEL was estimable for pentoxifylline only for 9/13 subjects for the reference product (Trt. A) and 4/13 subjects for the test product (Trt. B). For M1, KEL was estimable only for 6/13 subjects for the reference product (Trt. A) and 4/13 subjects for the test product (Trt. B).

4. Analytical

PAGES 5-7 PURGED
CONFIDENTIAL COMMERCIAL AND TRADE SECRET INFO

II. SINGLE DOSE FOOD STUDY

A. Study Sites

Clinical Site:

Principal Investigat
Co-Investigator:
Protocol: Comparative, Randomized, Single-Dose, Three-Way Crossover Bioavailability Study of Mylan and Hoechst-Roussel (Trental®) 400 mg Pentoxifylline Controlled-Release Tablets in Healthy Adult Males under Fed and Fasted Conditions (7/5/93; IRB approval 7/6/93)
Study #: Mylan #PENT-9327

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[2] Ambrus JL, Anain JM, Anain SM, et al. Dose-response effects of pentoxifylline on erythrocyte filterability: clinical and animal model studies. Clin Pharmacol Ther 1990;48:50-6.

Study Dates: Period 1 dosing, 7/22/93; Per. 2, 7/29/93; Per. 3 8/5/93
Analytical Site:

Analytical Director:
Analysis Dates: 8/9-24/93; storage period 35 days

B. Study Design

This was a randomized, single dose, three-way crossover design comparing 1) the test product pentoxifylline 400 mg extended-release tablet with the reference product Trental® 400 mg CR tablets under fed conditions, and 2) the test product under fasting and fed conditions, in 18 healthy male volunteers (15 completing) with a one week washout between treatments. Plasma was analyzed for the parent drug pentoxifylline (P) and the metabolite 5-hydroxypentoxifylline (M1).

C. Subject Selection

Eighteen subjects were selected for this study after signing informed consent according to the following criteria:

1. Inclusion Criteria

- males, 18-45 years old
- at least 60 kg and within ± 15% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983)
- good health as determined by medical history, physical examination, and laboratory values (hematology, serum chemistry, urinalysis, and HIV test)
- nonsmokers

2. Exclusion Criteria

- history or presence of significant systemic, organ, or psychiatric disease
- history or presence of hypersensitivity or idiosyncratic reaction to any xanthine, bleeding disorder, peptic ulcer, or alcoholism or drug abuse within the last year
- completion of another clinical trial in the four weeks prior to study start
- abnormal diet during the four weeks prior to study start
- excessive blood donation as described

D. Study Procedures

Treatments: After fasting ten hours prior to drug administration, subjects received one of the following treatments:

1) Treatment A (test, fasting), pentoxifylline 400 mg extended-release tablet, 1 X 400 mg, Mylan Lot #2Z012A

2) Treatment B (test, fed), pentoxifylline 400 mg extended-release tablet, 1 X 400 mg, Mylan Lot #2Z012A

3) Treatment C (reference, fed), Trental® 400 mg CR tablet, 1 X 400 mg, Hoechst-Roussel Lot #0787652

Each dose was administered with 240 ml of water. After a one week washout, each subject received the alternative treatment.

For treatments B and C, subjects received a standardized breakfast 30 minutes before dosing, consisting of one buttered English muffin, one fried egg, one slice of Canadian bacon, one slice of American cheese, one serving of hash brown potatoes, 180 ml of orange juice, and 240 ml of whole milk.

In Periods 1 and 3, the breakfast was served 30 minutes prior to drug administration. In Period 2, the breakfast was served 40 minutes prior to dosing.

Restrictions: Subjects were ambulatory during the study, and engaged in normal activity for the first 4 hours postdose, avoiding both strenuous exercise and complete rest. Subjects were confined to the clinical site from 12 hours predose until 24 hours postdose. No medications were allowed for the 7 days preceding the study. Alcohol and xanthine-containing beverages and foods were prohibited for 24 hours prior to dosing and during sample collection.

Meals and Fluids: Fluids were not allowed for two hours before or four hours after dosing (except for the 240 ml of water given with the dose, and the high-fat breakfast). Fasting occurred for ten hours prior to dosing, and standardized meals began four hours postdose.

Blood Sampling: Blood samples (10 ml, EDTA top Vacutainer) were collected at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, and 24 hours postdose. Samples were cooled in an ice bath and centrifuged under refrigeration. Plasma was stored at ≤ -12°.

E. Analytical Methodology and Data Analysis

F. Results

1. Product Information

1. **Formulation:** Table 1 (attached)

2. Clinical

1. **Completion:** Eighteen subjects were enrolled. Fifteen subjects completed all three study phases. Subject 7 was withdrawn prior to Period 2 dosing due to poor veins and refusal to complete the Period 2 breakfast. Subject 8 withdrew prior to Period 2 for personal reasons. Subject 15 did not return for Period 2 check-in.

2. **Protocol Deviations:**

- Collection Times: All blood draws were taken within 2 minutes of scheduled times, with the following exceptions: Trt. A, 8 samples, 3-11 minutes late; 2) Trt. B, 6 samples, 3-5 minutes late; 3) Trt. C, 14 samples, 3-15 minutes late. In one case (S18, Per. 2, 8 hours), the collection time was not recorded and was assumed to be at 8 hours postdose (taken within 16 minutes of scheduled time based on the time

the plasma sample was put in the freezer). The actual times of collection were used for calculations.

- Timing of Meal: In Period 2, dosing occurred 40 minutes after the meal was begun, due to final medical assessment of eligibility of subjects based on lab test results.

- Medications: S5 took multivitamins (Centrum® Forte) 6 days prior to Period 1 dosing.

3. **Adverse Events:**

- Three adverse events occurred which were judged possibly drug related. Subject 5 reported a headache twice in Period 1 (2 hours and 6.3 days postdose) and once in Period 2 (1 hour postdose). In the latter case, the intensity was moderate and S5 was given acetaminophen 500 mg tablet about 8 hours postdose.

- Six events were judged to be procedure-related: 1-2) S7, Per. 1, hematomas in forearms, mild intensity, treated with warm compresses; 3) S11, Per. 2, nausea at blood draw, moderate intensity; 4) S14, Per. 1, bruise on biceps, mild intensity; 5-6) S11, Per. 1, bruises on L/R fossa, mild intensity.

- Three events were judged as "other" causality: 1) S1, Per. 1 (1 hour postdose), back pain, mild intensity; 2) S4, Per. 2 (3 days postdose), sore throat, mild intensity; 3) S1, Per. 3 (7 hours postdose), axillary pain.

3. Pharmacokinetics/Statistics

1. Tables 7 and 8 show the reported mean plasma concentration vs. time profiles for pentoxifylline and M1, respectively. There were no nonzero predose concentrations for either analyte. There were no cases where the first nonzero concentration was the CMAX for either pentoxifylline or M1.

2. Tables 9 and 10 show the reported mean pharmacokinetic parameters for pentoxifylline and M1, respectively. The "residb" term was statistically significant ($p > 0.1$) for AUC(0-t) for both pentoxifylline and M1. For M1, there was a statistically significant treatment effect ($p < 0.05$) for AUC(0-t) for the B vs. C comparison. See Comment #1 below for reviewer's analysis.

Table 11 shows the ratios of least squares geometric means reported by the sponsor for pentoxifylline and M1. Table 12 shows the ratios of least squares geometric means for several conditions using the log-transformed data for AUC(0-t) and CMAX.

3. KEL was estimable for pentoxifylline only for 7/15 subjects for Trt. A, 8/15 subjects for Trt. B, and 8/15 subjects for Trt. C. For M1, KEL was estimable only for 10/15 subjects for Trt. A, 14/15 subjects for Trt. B, and 10/15 subjects for Trt. C.

4. Analytical

G. Comments

1. The sponsor analyzed the data using a residual model containing two terms for the first-order residual code. Mr. Don Schuirmann, Division of Biometrics, has commented previously on this type of model using contrast variables and suggested that the order of terms in the model be as follows: SUBJECT, PERIOD, TREATMENT, RESIDA, RESIDB.

Using the data supplied on diskette, the reviewer performed the following analyses with the GLM procedure of SAS on the log-transformed data for the parameters AUC(0-t) and CMAX:

- Condition 1: The data was analyzed with the standard model including all three treatments.

- Condition 2: The data was analyzed using a first-order residual model with the terms SEQUENCE, SUBJECT(SEQUENCE), PERIOD, TREATMENT, RES1. For both pentoxifylline and M1, the RES1 term was not statistically significant ($p > 0.1$) for either logAUC(0-t) or logCMAX.

- Condition 3: Because no residual effects were evident, the RES1 term was then dropped from the model and Trt. A was also dropped from the model. The data was then analyzed with the standard model.

The results are shown in Table 12. The reviewer's Condition 2 gives the same results as reported by the sponsor.

2. KEL was estimable only in 23/45 cases. As was the case in the fasting study, AUCINF should not be used a bioequivalence parameter for the food study.

3. The Analytical SOP is purged of many essential details.

4. The sponsor should explain why pentoxifylline standard curves BKO11 and BKO22 are both listed as Subject 5, Periods 1-3.

5. The inclusion criteria specify a weight within ± 15% of ideal body weight based on the Metropolitan Life tables. The sponsor did not include the tables in the submission. However, the Medical Demography Forms used for screening subjects (v. 1.4, p. 1481-following) state for all subjects that weight was within ± 15% of ideal weight.

III. MULTIPLE DOSE, STEADY-STATE STUDY

A. Study Sites

Clinical Site:

Principal Investigat
Co-Investigator:
Protocol: Comparative, Randomized, Steady-State, Two-Way Crossover Bioavailability Study of Mylan and Hoechst-Roussel (Trental®) 400 mg Pentoxifylline Controlled-Release Tablets in Healthy Adult Males (7/20/93; IRB approval 8/3/93)
Study #: Mylan #PENT-9328
Study Dates: Period 1 dosing, 8/1-3/93; Per. 2, 8/12-14/93
Analytical Site:

Analytical Director:
Analysis Dates: 8/20-9/1/93

B. Study Design

This was a randomized, multiple dose (q8h x 10 doses), steady-state, two-way crossover design comparing the test product pentoxifylline 400 mg extended-release tablet with the reference product Trental® 400 mg CR tablets under fasting conditions in 26 healthy male volunteers (25 completing) with an eight day washout between the last dose of Period 1 and the first dose of Period 2. Plasma was analyzed for the parent drug pentoxifylline (P) and the metabolite 5-hydroxypentoxifylline (M1).

C. Subject Selection

Twenty-six subjects (24 subjects plus two alternates) were selected for this study after signing informed consent according to the criteria below. Samples from subjects 1-24 were to be analyzed if the first 24 subjects completed the study. Alternates were chosen in order to obtain the same number of subjects per sequence when possible.

1. Inclusion Criteria

- males, 18-45 years old

- at least 60 kg and within ± 15% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983)
- good health as determined by medical history, physical examination, and laboratory values (hematology, serum chemistry, urinalysis, and HIV test)
- nonsmokers

2. Exclusion Criteria

- history or presence of significant systemic, organ, or psychiatric disease
- history or presence of hypersensitivity or idiosyncratic reaction to any xanthine, bleeding disorder, peptic ulcer, or alcoholism or drug abuse within the last year
- completion of another clinical trial in the four weeks prior to study start
- abnormal diet during the four weeks prior to study start
- excessive blood donation as described

D. Study Procedures

Treatments: After fasting ten hours prior to drug administration, subjects received one of the following treatments:

1) Treatment A (test), pentoxifylline 400 mg extended-release tablet, 1 X 400 mg q8h for 10 doses, Mylan Lot #2Z012A

2) Treatment B (reference, fed), Trental® 400 mg CR tablet, 1 X 400 mg q8h for 10 doses, Hoechst-Roussel Lot #0787652

Dosing times were 7AM, 3PM, and 11PM. Each dose was administered with 240 ml of water.. After an eight day washout between the last dose of Period 1 and the first dose of Period 2, each subject received the alternative treatment.

Restrictions: Subjects were ambulatory during the study, and engaged in normal activity for the first 4 hours postdose, avoiding both strenuous exercise and complete rest. Subjects were confined to the clinical site from 12 hours before initial dosing until after the 8-hour draw on Day 4. No medications were allowed for the 7 days preceding the study. Alcohol and xanthine-containing beverages and foods were prohibited for 24 hours prior to dosing and during sample collection.

Meals and Fluids: Water was not allowed for two hours before or four hours after dosing on Day 4, but was allowed at all other times. Fasting occurred overnight prior to dosing, and for four hours postdose on Day 4. Standardized meals were provided at 4 and 9 hours postdose on Day 4, and at about 1, 4, and 9 hours after initial dosing on Days 1-3.

Blood Sampling: Blood samples (10 ml, EDTA Vacutainer) were collected at 0 hours (predose on Day 1); before the first doses on Day 2 (predose 4, 24 hours), Day 3 (predose 7, 48 hours), and Day 4 (predose 10, 72 hours); and, after the tenth dose at 72.25, 72.5, 73, 73.5, 74, 74.5, 75, 75.5, 76, 76.5, 77, 78, and 80 hours. Samples were cooled in an ice bath and centrifuged under refrigeration. Plasma was stored at ≤ -12°. All blood draws were taken within 2 minutes of scheduled times

E. Analytical Methodology and Data Analysis

F. Results

1. Product Information

1. **Formulation:** Table 1 (attached)

2. Clinical

1. **Completion:** Twenty-six subjects were enrolled. Twenty-five subjects completed both study phases. Subject 26 withdrew prior to Period 2 check-in due to personal reasons. Samples were analyzed from the first 24 subjects as per protocol.

2. **Protocol Deviations:** Subjects 7, 19, and 24 consumed xanthine-containing beverages (cola, coffee, hot chocolate) 20-24 hours before Period 2 dosing. The reviewer concurs these deviations are not likely to affect the study outcome.

3. **Adverse Events:** No events were judged as serious or required any medication.

- Subject 17 experienced burning sensations in the chest and heart palpitations (five events of mild intensity) on several occasions: 3.5 hr and 7 hr postdose #3 on Day 1, Per. 1; 5 hr postdose #7 on Day 3, Per. 1. The Medical Designate noted a normal exam with thoracic muscular skeletal pain, and that forceful ejection was probably due to study medication but was not a contraindication to continued dosing. Resolution was complete by 7.5 hr postdose #10 on day 4, Per. 1.

- Three events were judged to be not drug or procedure related and of mild intensity: leg pain (1), foot blister (1), pimples (1).

- Ten events were judged to be drug related: headache (3), insomnia (1), pinching sensation in limbs (1), heart palpitations (2), tightness in throat (1), pimples (1), vomiting (1). All events were rated as mild intensity except for S10, heart palpitations of moderate intensity (four episodes from 10.3-18.2 hr postdose #3, Day 1).

- Two events were judged to be procedure related and of mild intensity: pain at venipuncture site (1), with application of ice; bruise at venipuncture site (1).

3. Pharmacokinetics/Statistics

1. Tables 13 and 14 show the reported mean plasma concentration vs. time profiles for pentoxifylline and M1, respectively. There were no nonzero predose (0 hr, dose #1) concentrations for either analyte. There were two cases where the first sampling time (72.25 hr) after the last dose (dose #10, 72 hr) was the CMAX for pentoxifylline (Trt. B, S3 and S5).

2. Tables 15 and 16 show the reported mean pharmacokinetic parameters for pentoxifylline and M1, respectively. These data exclude S16 and the Per. 2, 4.5 hr pentoxifylline plasma

concentration for S6. For pentoxifylline, there were no statistically significant sequence ($p > 0.1$), treatment ($p > 0.05$), or period ($p > 0.05$) effects for $AUC_{0-\tau}$, CMAX, or their log-transformed values. For M1, there were statistically significant treatment effects ($p < 0.05$) for $AUC_{0-\tau}$ and $logAUC_{0-\tau}$.

Using the data supplied on diskette, the reviewer used the GLM procedure of SAS to produce values of the adjusted estimate of treatment difference and its S.E. for calculation of the 90% CI. The results are shown in Table 17.

3. The results for S16 were excluded based on the MNR test for outliers when applied to CMAX. Meaningful values for pentoxifylline CMIN, FLUX1, and FLUX2 could not be obtained for S16 in Per. 1; these values were set to "missing" for the statistical analysis.

4. The Per. 2, 4.5 hr pentoxifylline concentration value for S6 was also excluded from the analyses as an outlier based on the MNR test. If this value is excluded, $AUC_{0-\tau}$ = 871 ng*hr/ml and CMAX = 174.41 ng/ml. If this value is included, $AUC_{0-\tau}$ = 955 ng*hr/ml and CMAX = 296.02 ng/ml.

4. Analytical

G. Comments

3. To determine whether steady-state conditions had been reached, the sponsor performed ANOVA with a model containing terms for subject and day for every treatment-period combination. There were no statistically significant day effects ($p > 0.05$), and the sponsor interpreted this finding that steady-state had been achieved.

The Division currently has no guidelines for determination of steady-state conditions in multiple dose studies. The sponsor's analysis is limited to the finding that mean concentration values for each period-treatment combination do not differ significantly from each other over the three days, and provides no information as to whether any subject-treatment combination has reached steady-state. It is possible that the REG procedure of SAS might be used to determine if slopes through the three CMIN values were significantly different from zero for each subject-treatment combination.

The reviewer consulted with Dr. Tsai Lin, Division of Biometrics, who suggested using a repeated measures type of statistical model: SEQ, SUBJ(SEQ), TRT, SEQ*TRT, SUBJ*TRT(SEQ), DAY, DAY*SEQ, SUBJ*DAY(SEQ), TRT*DAY, SEQ*TRT*DAY. The reviewer attempted ANOVA with the GLM procedure of SAS; however, computer memory was insufficient to run this model. By replacing SEQ*TRT with PER, the ANOVA was done for the parameter CMIN with the following results: 1) the TRT*DAY term had $p = 0.1246$ when tested against the MSE, which may or may not be statistically significant ($p > 0.1$ or $p > 0.15$?); 2) the DAY term had $p = 0.125$ when tested against SUBJ*DAY(SEQ) as the error term, which may or may not be statistically significant. Dr. Lin's conclusion was that it should not be stated that the DAY effect has no statistical significance; in other words, there may be some doubt that steady-state conditions existed if this procedure is used. If log-transformed CMIN is analyzed by the same procedure, the DAY effect is not statistically significant ($p = 0.2521$).

Since the TRT*DAY effect may be significant for CMIN, the reviewer also performed ANOVA with model containing only terms for SUBJ and DAY in which treatments were considered separately. For Treatments 1 (test) and 2 (reference), the p values for the DAY effect were 0.3473 and 0.0622, respectively. Therefore, for the reference product, there was a statistically significant DAY effect ($p < 0.1$) which might indicate the absence of steady-state conditions.

4. The inclusion criteria specify a weight within ± 15% of ideal body weight based on the Metropolitan Life tables. The sponsor did not include the tables in the submission. However, the Medical Demography Forms used for screening subjects (v. 1.6, p. 2747-following) state for all subjects that weight was within ± 15% of ideal weight.

5. The Analytical Method SOP is purged of many essential details.

IV. DEFICIENCIES

A. For the single dose fasting study:

1. For pentoxifylline, there were seven cases where the first nonzero concentration (at the first sampling time of 0.5 hr) was the CMAX: Trt. A (ref.), Subjects 8, 11, 12; Trt. B (test), Subjects 4, 7, 8, and 12. The Division considers these results to be unacceptable for use in bioequivalence determination. If these five subjects are excluded, only eight subjects remain, and the resulting 90% CI for logCMAX is 95.5-133.1 which is outside of the allowable equivalence interval of 80-125%. For future studies, the sponsor may consider a sampling time of 0.25 hr.

B. For the single dose food study:

2. The sponsor should explain why pentoxifylline standard curves BK011 and BK022 are both listed as Subject 5, Periods 1-3.

C. For the multiple dose study:

3. The Division does not accept the exclusion of data based solely on the results of a statistical test for outliers. If ANOVA is performed including the pentoxifylline data from S16 and the Per. 2, 4.5 hr, concentration for S6, the 90% CI's for $\log AUC_{0-\tau}$ and logCMAX are 81.0-96.9 and 72.9-96.8, respectively. The 90% CI for log-transformed CMAX is outside of the acceptable equivalence interval of 80-125%.

V. RECOMMENDATIONS

1. The bioequivalence study (single dose, fasting conditions) conducted by Mylan Pharmaceuticals on its pentoxifylline extended-release 400 mg tablet, lot #2Z012A, comparing it to Hoechst-Roussel's Trental® 400 mg tablet, lot #0787652, has been found unacceptable by the Division of Bioequivalence due to deficiency #1 stated above.

2. The bioequivalence study (single dose, fed conditions) conducted by Mylan Pharmaceuticals on its pentoxifylline extended-release 400 mg tablet, lot #2Z012A, comparing it to Hoechst-Roussel's Trental® 400 mg tablet, lot #0787652, has been found incomplete by the Division of Bioequivalence due to deficiency #2 stated above.

3. The bioequivalence study (multiple dose, fasting conditions) conducted by Mylan Pharmaceuticals on its pentoxifylline extended-release 400 mg tablet, lot #2Z012A, comparing it to

Hoechst-Roussel's Trental® 400 mg tablet, lot #0787652, has been found unacceptable by the Division of Bioequivalence due to deficiency #3 stated above.

4. The sponsor should be aware that necessary information was missing from all three studies:

- Certificates of analysis or other documentation stating the potencies of the biostudy lots of test (Mylan Lot #2Z012A) and reference (Hoechst-Roussel Lot #0787652) products

- Dissolution data: The sponsor is referred to the Division of Bioequivalence Guidance "Oral Extended Release Dosage Forms: in vivo Bioequivalence and in vitro Dissolution Testing" (9/9/93) for information concerning dissolution testing.

- Theoretical and finished batch sizes and manufacturing dates for the test product biostudy lot (Mylan #2Z012A)

- The specific weight tables used by the sponsor to determine subject eligibility according to the protocols, with allowable weight ranges included (± 10% for the single dose fasting study, ± 15% for the two other studies)

- The Analytical Method SOP sections are purged of many essential details, which must be submitted for the study to be considered complete.

5. In v. 1.1, p. 367, the sponsor states that Mylan "authorized the metabolite assay as required for submission of this study". However, the sponsor does not refer to any conversation or communication from any FDA source which states that only the parent drug and M1 are required for bioequivalence studies of this drug. The Division is currently considering adoption of a Guidance for Bioequivalence Studies of Pentoxifylline Extended-Release Tablets. This guidance proposes to require the measurement of unchanged pentoxifylline, the M1 metabolite, and another metabolite, 1-(4-carboxypropyl)-3,7-dimethylxanthine or M5. The Division advises that measurement of parent drug, M1, and M5 will be required for future studies until the Guidance is issued where final requirements will be stated.

6. For future multiple dose studies, the sponsor may wish to try the following procedures:

- The REG procedure of SAS may be used to determine if slopes through the three CMIN values are significantly different from zero. This may provide information as to whether any subject-treatment combination has reached steady-state.

- In addition, for possible evaluation of steady-state conditions, the sponsor may use a model including the terms SEQ, SUBJ(SEQ), PER, TRT, SUBJ*TRT(SEQ), DAY, SEQ*DAY, SUBJ*DAY(SEQ), PER*DAY, and TRT*DAY. The TRT and PER terms are tested against SUBJ*TRT(SEQ) as the error term. The DAY and SEQ*DAY terms are tested against SUBJ*DAY(SEQ) as the error term. If the TRT*DAY term is statistically significant ($p < 0.1$ suggested), then the data may be analyzed for each treatment separately using a model consisting of SUBJ and DAY terms.

7. The firm should be informed of deficiencies 1-3 and recommendations 1-6.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

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Concur: _____ Date 8/13/94
Ramakant M. Mhatre, Ph.D.
Acting Director
Division of Bioequivalence

JDH/crc/6-30-94/74425

cc: ANDA #74-425 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

Table 1 - Formulation of the Test Product

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Component	mg / tablet
Core	
pentoxifylline	400.0
povidone, USP	
purified water, USP	
hydroxyethylcellulose, NF	
microcrystalline cellulose, NF	
magnesium stearate, NF	
Film Coat	
Solids	
purified water, USP	

Table 2 - Mean Reported Plasma Concentrations (ng/ml) of Pentoxifylline (Single Dose, Fasting Study, N = 13)

Time (hr)	Trt. A (ref.)	CV (%)	Trt. B (test)	CV (%)	% Diff.
0	0.00	-	0.00	-	-
0.5	78.04	48.9	73.28	57.8	-6.10
1	79.3	58.7	80.2	52.0	1.13
1.5	79.02	58.8	71.1	49.8	-10.02
2	76.17	62.6	77.27	63.0	1.44
2.5	66.62	53.6	79.44	58.2	19.24
3	58.86	59.0	64.86	63.2	10.19
3.5	48.67	64.7	51.31	63.6	5.42
4	39.86	51.8	44.28	64.8	11.09
4.5	37.99	65.2	41.65	62.4	9.63
5	34.96	69.2	37.29	62.0	6.66
6	50.81	59.5	60.38	63.5	18.83
8	39.19	54.8	44.67	60.3	13.98
10	43.12	48.2	44.37	64.6	2.90
12	37.7	58.7	44.99	61.4	19.34
16	15.48	84.6	15.99	64.0	3.29
24	2.4	182	0.00	-	-

Table 3 - Mean Reported Plasma Concentrations of M1 (ng/ml, Single Dose, Fasting Study, N = 13)

Time (hr)	Trt. A (ref.)	CV (%)	Trt. B (test)	CV (%)	% Diff.
0	0.00	-	0.00	-	-
0.5	97.8	60.6	85.18	65.2	-12.90
1	171.17	47.4	167.55	37.4	-2.11
1.5	203.45	49.0	198.18	34.4	-2.59
2	217.33	43.2	215.6	34.3	-0.80
2.5	230.68	44.0	221.14	38.1	-4.14
3	216.99	47.5	221.36	41.6	2.01
3.5	207.56	48.4	214.52	46.2	3.35
4	198.98	57.7	194.55	50.8	-2.23
4.5	181.33	53.7	182.82	58.0	0.82
5	179.18	52.6	168.65	57.1	-5.88
6	155.71	49.7	163.52	43.2	5.02
8	107.79	42.3	128.15	42.8	18.89
10	116.02	41.7	111.67	41.8	-3.75
12	124.64	43.2	128.07	57.5	2.75
16	72.25	77.6	74.77	51.9	3.49
24	11.65	156	4.57	158	-

Trt. A = Trental® 400 mg CR tablet (Hoechst Roussel)
Trt. B = pentoxifylline 400 mg ER tab (Mylan)

Table 4 - Mean Reported Pharmacokinetic Parameters of Pentoxifylline (Single Dose, Fasting Study, N = 13)

Parameter	Trt. A (ref.)	CV (%)	Trt. B (test)	CV (%)	%Diff. or Ratio[1]	90% CI
AUC(0-t)[2]	721.8	54.6	747.6	50.0	3.57	92.7-115.6
lnAUC(0-t)	-	-	-	-	1.027	89.9-117.4
AUCINF	921.5	50.3[4]	1120.6	28.7[5]	21.61	-
lnAUCINF	-	-	-	-	-	-
CMAX (ng/ml)	100.54	46.8	103.51	44.6	2.95	90.2-117.4
lnCMAX	-	-	-	-	1.022	84.9-123.0
TMAX (hr)	1.423	55.3	1.731	85.5	21.64	-
KEL (hr^{-1})	0.1487	31.1[4]	0.197	37.8[5]	32.48	-
HALF (hr)	5.039	28.0	4.122	53.1	-18.20	-

Table 5 - Mean Reported Pharmacokinetic Parameters of M1 (Single Dose, Fasting Study, N = 13)

Parameter	Trt. A (ref.)	CV (%)	Trt. B (test)	CV (%)	% Diff or Ratio[1]	90% CI
AUC(0-t)[2]	2411.9	51	2387.8	43	-1.00	87.0-112.9
lnAUC(0-t)	-	-	-	-	1.015	90.8-113.4
AUCINF	3542.4	33[5]	2710.1	53[4]	-23.50	-
lnAUCINF	-	-	-	-	-	-
CMAX	243.62	44	243.92	42	0.12	86.7-114.9
lnCMAX	-	-	-	-	1.004	87.6-115.0
TMAX (hr)	2.423	40	2.885	43	19.07	-
KEL (hr^{-1})	0.1508	43	0.1951	17	29.38	-
HALF (hr)	5.359	43	3.652	21	-31.85	-

[1] untransformed: % diff. = (T - R)*100/R where T and R are the arithmetic means; log-transformed: ratio of geometric means = exp(logT - logR), where (logT - logR) is the estimate from the ANOVA

[2] units for AUC's, ng*hr/ml [3] units for CMAX, ng/ml

[4] N = 9 [5] N = 4 [6] N = 6

Trt. A = Trental® 400 mg CR tablet (Hoechst Roussel)
Trt. B = pentoxifylline 400 mg ER tab (Mylan)

Table 6 - Assay Method Validation

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Table 6 - Assay Method Validation (continued)

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Table 7 - Mean Reported Plasma Concentrations of Pentoxifylline (Food Study, N = 15)

Time (hr)	Trt. A mean, ng/ml	(test, fasted) CV (%)	Trt. B mean, ng/ml	(test, fed) CV (%)	Trt. C mean, ng/ml	(ref., fed) CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
0	0.00	-	0.00	-	0.00	-	-	-
0.25	18.089	93.2	9.154	143	13.496	188	-32.17	-49.39
0.5	51.343	50.8	26.863	106	32.413	103	-17.12	-47.68
1	56.553	49.8	46.107	83.7	51.725	72.3	-10.86	-18.47
1.5	70.497	67.9	54.445	59.5	57.069	49.6	-4.60	-22.77
2	64.443	73.3	65.361	53.1	68.322	73.5	-4.33	1.42
2.5	48.547	70.7	74.649	52.9	72.245	61	3.33	53.77
3	45.198	66.9	78.45	52.5	77.32	66.8	1.46	73.57
3.5	44.251	63.5	81.86	54	75.379	58.5	8.60	84.99
4	40.497	68.3	76.264	63.5	72.983	64.5	4.50	88.32
4.5	56.705	75.8	131.83	70.3	131.84	88.5	-0.01	132.48
5	42.556	59.6	88.391	66.2	80.325	85.1	10.04	107.71
5.5	39.317	61.1	78.98	90.5	82.481	111	-4.24	100.88
6	37.643	50.6	91.895	154	104.98	134	-12.46	144.12
7	33.515	50.8	95.184	144	67.309	137	41.41	184.00
8	27.589	65.8	54.301	130	49.897	102	8.83	96.82
10	31.594	56.5	29.541	97.2	35.459	121	-16.69	-6.50
12	21.066	65.9	15.394	85.6	19.6	85[1]	-21.50	-26.92
14	18.676	73.9	8.328	111	11.557	97.4	-27.94	-55.41
16	13.007	91.4	4.112	138	5.219	167	-21.21	-68.39
20	2.816	229	0.333	387	0.578	387	-42.39	-88.17
24	1.705	229	0.00	-	0.00	-	-	-

[1] N = 14

Trt. A = pentoxifylline (Mylan, fasting), 1 X 400 mg
Trt. B = pentoxifylline (Mylan, fed), 1 X 400 mg
Trt. C = Trental® (Hoechst, fed), 1 X 400 mg

Table 8 - Mean Reported Plasma Concentrations of M1 (Food Study, N = 15)

Time (hr)	Trt. A mean, ng/ml	CV (%)	Trt. B mean, ng/ml	CV (%)	Trt. C mean, ng/ml	CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
0	0.00	-	0.00	-	0.00	-	-	-
0.25	17.35	118	5.01	185	19.29	260	-74.03	-71.12
0.5	86.41	62	32.48	113	44.62	126	-27.21	-62.41
1	174.1	40	96.91	82	118.28	74	-18.07	-44.35
1.5	247.4	35	139.44	66	168.65	54	-17.32	-43.64
2	277.7	48	189.73	59	209.52	48	-9.45	-31.69
2.5	289.1	51	245.17	63	242.76	47	0.99	-15.18
3	268.7	52	299.6	58	289.03	49	3.66	11.50
3.5	259.4	52	335.37	52	325.43	45	3.05	29.27
4	244.2	51	355.73	49	329.69	49	7.90	45.70
4.5	225.6	57	404.07	48	410.41	55	-1.54	79.09
5	201.0	49	373.25	50	372.99	68	0.07	85.72
5.5	181.6	50	336.4	56	351.25	76	-4.23	85.28
6	165.5	46	342.51	71	348.08	83	-1.60	106.94
7	153.2	44	322.36	90	328.47	100	-1.86	110.42
8	130.7	39	264.54	102	262.11	98	0.93	102.42
10	132.4	52	151.09	78	171.73	78	-12.02	14.15
12	102.5	47	86.13	70	114.59	79	-24.84	-15.96
14	83.31	53	53.86	89	68.18	87	-21.00	-35.35
16	70.46	77	33.7	94	39.39	112	-14.45	-52.17
20	32.35	131	9.65	125	10.55	171	-8.53	-70.17
24	11.16	148	0.7	387	4.45	180	-84.27	-93.73

Trt. A = pentoxifylline (Mylan, fasting), 1 X 400 mg
Trt. B = pentoxifylline (Mylan, fed), 1 X 400 mg
Trt. C = Trental® (Hoechst, fed), 1 X 400 mg

Table 9 - Mean Reported Pharmacokinetic Parameters of Pentoxifylline (Food Study, N = 15, Arithmetic Means)

Parameter	Trt. A (mean)	CV (%)	Trt. B (mean)	CV (%)	Trt. C (mean)	CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
AUC(0-t)	559.5	60	751.7	73	755.6	75	-0.52	34.35
AUCINF	749.3	60[1]	915.2	76[2]	940	75[2]	-2.64	22.14
CMAX	88.85	55	170.21	74	161.92	79	5.12	91.57
TMAX (hr)	1.737	86	4.767	44	4.617	47	3.25	174.44
KEL (hr^{-1})	0.1841	22[1]	0.2635	48[2]	0.4138	62[2]	-36.32	43.13
T½ (hr)	3.927	23[1]	3.077	38[2]	2.223	51[2]	38.42	-21.65

Table 10 - Mean Reported Pharmacokinetic Parameters of M1 (Food Study, N = 15, Arithmetic Means)

Parameter	Trt. A (mean)	CV (%)	Trt. B (mean)	CV (%)	Trt. C (mean)	CV (%)	% Diff. (B v. C)	% Diff. (B v. A)
AUC(0-t)	2675.3	49	3066	53	3259.5	55	-5.94	14.60
AUCINF	2447.2	45[3]	3185.1	52[4]	3965.3	47[3]	-19.68	30.15
CMAX	307.66	48	505.85	51	499.75	55	1.22	64.42
TMAX (hr)	2.333	24	5.47	36	5.139	41	6.44	134.46
KEL (hr^{-1})	0.2115	31[3]	0.3436	60[4]	0.4512	33[3]	-23.85	62.46
T½ (hr)	3.673	41[3]	2.869	65[4]	1.697	33[3]	69.06	-21.89

Tables 9 & 10: [1] N = 7 [2] N = 8 [3] N = 10 [4] N = 14

Table 11 - Least Squares Means and Ratios for Pentoxifylline and M1 as Reported (Food Study, N = 15)

Drug	Parameter	Trt. A	Trt. B	Trt. C	Ratio[1]
Pent.	AUC(0-t)	560.2	715.9	790.7	90.5
	logAUC(0-t)	-	-	-	98.1
	CMAX	89.775	160.55	170.64	94.1
	logCMAX	-	-	-	107.8
M1	AUC(0-t)	2663.7	2989.1	3348	89.3
	logAUC(0-t)	-	-	-	93.6
	CMAX	316.2	485.33	511.72	94.8
	logCMAX	-	-	-	103.1

[1] untransformed: ratio (as %) = Trt. B_{LSM} / Trt. C_{LSM}; log-transformed: ratio (as %) of geometric means = exp(logB - logC), where (logB - logC) is the estimate from the ANOVA

units for AUC's: ng*hr/ml; units for CMAX: ng/ml

Trt. A = pentoxifylline (Mylan, fasting), 1 X 400 mg
Trt. B = pentoxifylline (Mylan, fed), 1 X 400 mg
Trt. C = Trental® (Hoechst, fed), 1 X 400 mg

Table 12 - Ratios of Least Squares Geometric Means as Determined by the Reviewer (Food Study, N = 15)

Analyte	Condition	Ratio - AUC(0-t)	Ratio - CMAX
Pent.	1	1.005	1.076
	2	0.981	1.078
	3	1.002	1.084
M1	1	0.959	1.02
	2	0.936	1.031
	3	0.947	1.016

Condition:

1 Standard model, all three treatments included

2 Residual model, all three treatments included

3 Standard model, only Treatments B and C included

Table 13 - Mean Reported Plasma Concentrations of Pentoxifylline (ng/ml, Multiple Dose Study, N = 23)[1]

Time (hr)	Trt. A (mean)	(test) CV (%)	Trt. B (mean)	(ref.) CV (%)	% Diff.
0	0.00	-	0.00	-	0.00
24	43.96	55	49.2	37	-10.65
48	49.59	45	44.44	40	11.59
72	50.16	46	56.26	53	-10.84
72.25	68.11	37	78.32	43	-13.04
72.5	107.8	41	114.47	38	-5.83
73	99.57	40	111.18	42	-10.44
73.5	93.37	41	98.37	40	-5.08
74	76.44	38	85.96	31	-11.07
74.5	63.27	34	78.64	42	-19.54
75	61.05	41	66.34	35	-7.97
75.5	53.91	41	61.6	39	-12.48
76	46.76	37	52.94	38	-11.67
76.5	69.83	42	76.86	36	-9.15
77	65.43	50	70.89	53	-7.70
78	52.34	52	55.08	55	-4.97
80	32.4	41	37.14	53	-12.76

[1] N = 23 (S16 deleted by sponsor as outlier based on MNR test)

Trt. A = pentoxifylline 400 mg ER tablet (Mylan)
Trt. B = Trental® 400 mg CR tablet (Hoechst-Roussel)

Table 14 - Mean Reported Plasma Concentrations of M1 (ng/ml, Multiple Dose Study, N = 24)

Time (hr)	Trt. A (mean)	(test) CV (%)	Trt. B (mean)	(ref.) CV (%)	% Diff.
0	0.00	-	0.00	-	0.00
24	238.6	50	254.85	45	-6.38
48	287.41	53	258.62	42	11.13
72	246.16	45	290.5	55	-15.26
72.25	261.81	38	302.28	48	-13.39
72.5	340.77	34	385.12	46	-11.52
73	428.67	36	473.59	43	-9.49
73.5	449.95	35	483.64	39	-6.97
74	447.36	36	479.07	41	-6.62
74.5	427.19	39	452.92	39	-5.68
75	388.24	37	429.95	39	-9.70
75.5	363.17	40	393.02	36	-7.60
76	329.78	39	361.11	36	-8.68
76.5	307.41	36	339.5	37	-9.45
77	287.39	41	325.56	38	-11.72
78	234.05	41	257.39	37	-9.07
80	167.87	47	182.26	45	-7.90

Trt. A = pentoxifylline 400 mg ER tablet (Mylan)
Trt. B = Trental® 400 mg CR tablet (Hoechst-Roussel)

Table 15 - Mean Reported Pharmacokinetic Parameters of Pentoxifylline (Multiple Dose Study, N = 23)[1]

Parameter	Trt. A mean (LSM)[2]	test CV (%)	Trt. B mean (LSM)	ref. CV (%)	% Diff. or Ratio[3]	90 % CI
$AUC_{0-\tau}$ (ng*hr/ml)	505.8 (506.6)	35	559.5 (560.6)	35	-9.60	81.8-99.0
$logAUC_{0-\tau}$	-	-	-	-	0.905	82.9-98.8
CMAX (ng/ml)	118.02 (117.97)	35	131.16 (130.72)	34	-10.02	78.5-102.0
logCMAX	-	-	-	-	0.899	80.2-100.8
CMIN (ng/ml)	29.29	36	32.23	46	-9.12	-
TMAX (hr)	1.109	82	1.435	107	-22.72	-
FLUX1[4] (%)	142.31	24	146.36	29	-2.77	-
FLUX2[5] (%)	322.08	40	416.57	88	-22.68	-

1 N = 23 (S16 deleted by sponsor as outlier based on MNR test)
2 mean = arithmetic mean, LSM = least squares mean from ANOVA
3 untransformed: % diff. = (T - R)*100/R where T and R are the arithmetic means; log-transformed: ratio of geometric means = exp(logT - logR), where (logT - logR) is the estimate from the ANOVA
4 FLUX1 = (CMAX - CMIN) * 100 / ($AUC_{0-\tau}$ / γ)
5 FLUX2 = (CMAX - CMIN) * 100 / CMIN

Trt. A = pentoxifylline 400 mg ER tablet (Mylan)
Trt. B = Trental® 400 mg CR tablet (Hoechst-Roussel)

Table 16 - Mean Reported Pharmacokinetic Parameters of M1
(Multiple Dose Study, N = 24)

Parameter	Trt. A mean[1]	test CV (%)	Trt. B mean	ref. CV (%)	% Diff. or Ratio[2]	90 % CI
$AUC_{0-\gamma}$ (ng*hr/ml)	2529.4	34	2775.2	37	-8.86	84.2-98.1
$logAUC_{0-\gamma}$	-	-	-	-	0.921	86.3-98.3
CMAX (ng/ml)	474.73	35	515.82	39	-7.97	83.2-100.8
logCMAX	-	-	-	-	0.928	86.5-99.5
CMIN (ng/ml)	155.27	49	173.61	45	-10.56	-
TMAX (hr)	1.625	44	1.813	52	-10.37	-
FLUX1[3] (%)	102.09	25	99.92	22	2.17	-
FLUX2[4] (%)	275.93	126	242.05	82	14.00	-

[1] for N=24 (balanced study), the arithmetic mean = LSM

[2] untransformed: % diff. = (T - R)*100/R where T and R are the arithmetic means; log-transformed: ratio of geometric means = exp(logT - logR), where (logT - logR) is the estimate from the ANOVA

[3] FLUX1 = (CMAX - CMIN) * 100 / ($AUC_{0-\gamma}$ / γ)

[4] FLUX2 = (CMAX - CMIN) * 100 / CMIN

Trt. A = pentoxifylline 400 mg ER tablet (Mylan)
Trt. B = Trental® 400 mg CR tablet (Hoechst-Roussel)

Table 17 - Comparison of 90% CI Values, Multiple Dose Study

Condition	N	90% CI - $\log AUC_{0-\tau}$	90% CI - logCMAX
Pentoxifylline			
1	23	82.9-98.8	80.2-100.8
1	24	81.0-96.9	72.9-96.8
2	23	82.9-98.8	80.2-100.8
2	24	80.9-96.9	72.9-96.8
M1			
1	24	86.3-98.3	86.5-99.5
2	24	86.3-98.3	86.5-99.5

Condition 1 90% CI calculated using estimate and its S.E. from the GLM results in the submission

2 90% CI calculated using the data supplied on diskette and the reviewer's GLM analysis