

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75028

APPROVAL LETTER

JUL 20 1998

Keller and Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Laboratories, Inc.
1001 G Street N.W., Suite 500 West
Washington, DC 20001



Dear Sir:

This is in reference to your abbreviated new drug application dated December 16, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Pentoxifylline Extended-release Tablets, 400 mg.

Reference is also made to your amendments dated October 29, 1997; and February 12, April 9, June 15, June 17, and July 10, 1998.

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 proposed in your application.

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 and 314.98. 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.

Page 2

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

u T'
7-20-98

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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DRAFT FINAL PRINTED LABELING

1998

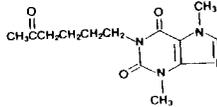
Pentoxifylline[®]

Extended-release Tablets, 400 mg

DESCRIPTION

Pentoxifylline Extended-release Tablets for oral administration, contains 400 mg of the active drug and the following inactive ingredients: hydroxyethyl cellulose NF, povidone USP, talc USP, magnesium stearate NF, isopropyl alcohol USP in an extended-release formulation. Pentoxifylline is a tri-substituted xanthine derivative designated chemically as 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione that, unlike theophylline, is a hemorrheologic agent, i.e. an agent that affects blood viscosity. Pentoxifylline is freely soluble in chloroform, soluble in water and soluble in methanol.

The structural formula is:



Molecular weight: 278.31

Molecular formula: C₁₃H₁₈N₄O₅

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. 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-dimethylxanthine) 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-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (Cytochrome P₂₉) 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 Extended-release Tablets 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 the 400 mg extended-release pentoxifylline tablet, plasma levels of the parent compound and its metabolites reach their maxima within 2 to 4 hours and remain constant over an extended period of time. Coadministration of Pentoxifylline extended-release tablets with meals resulted in an increase in mean C_{max} and AUC by about 28% and 13% for pentoxifylline, respectively. C_{max} for metabolite M1 also increased by about 20%. 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 Extended-release Tablets 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.

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 examination for bleeding including hematocrit and/or hemoglobin. Concomitant administration of pentoxifylline and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals. Such patient should be closely monitored for signs of toxicity and have their theophylline dosage adjusted as necessary. 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, 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 finding 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: Pregnancy 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 daily 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.

INCIDENCE (%) OF SIDE EFFECTS

	Extended-Release Tablets		Immediate-Release Capsules	
	Commercially Available	Used only for Controlled Clinical Trials	Used only for Controlled Clinical Trials	
			Pentoxifylline Extended-Release Tablets	Placebo
(Nos. 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 Extended-release Tablet 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 reactions; Digestive - hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic - decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

OVERDOSAGE

Overdosage with Pentoxifylline Extended-release Tablet has been reported in pediatric patients 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 4-5 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 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 Extended-release Tablets should be discontinued.

HOW SUPPLIED

Pentoxifylline Extended-release Tablets, are available for oral administration as 400 mg white, oblong, compressed tablets, engraved with "BVF" on one side and "0117" on the other, tablets are unscored; supplied in bottles of 100 (NDC 0093-5116-01)

Store at controlled room temperature 15°-30°C (59-86°F).

Dispense in well-closed, light-resistant containers with safety closures

Caution. Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured for:
TEVA PHARMACEUTICALS USA
Sellersville, PA
18960

Manufactured by:
Biovail Corporation International
Mississauga, Ontario
Canada L5L 1J9

Rev. 06/98

LB-0003-00

PRINTED CONTAINER LABELS



N 3 0093-5116-01 3

Printed in U.S.A.

NDC 0093-5116-01

PENTOXIFYLLINE
Extended-release
Tablets
400 mg

Each tablet contains:
Pentoxifylline 400 mg

Take with meals

Rx only



100 TABLETS



Do not use if bottle closure seal is broken.
Usual Dosage: See insert for full prescribing information.
Dispense in well-closed, light-resistant containers with safety closures.
Store at controlled room temperature 15 - 30°C (59 - 86°F).
KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.
Manufactured By:
Biovail Corporation International
Mississauga, Ontario
Canada L5L 1J9
LL-0157-00/iss. 5/98



N 3 0093-5116-01 3

Printed in U.S.A.

NDC 0093-5116-01

PENTOXIFYLLINE
Extended-release
Tablets
400 mg

Each tablet contains:
Pentoxifylline 400 mg

Take with meals

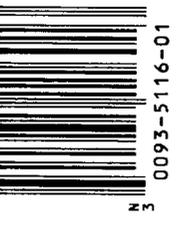
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N 3 0093-5116-01 3

Printed in U.S.A.

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Extended-release
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Mississauga, Ontario
Canada L5L 1J9
LL-0157-00/iss. 5/98

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75028

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3
2. ANDA # 75-028
3. NAME AND ADDRESS OF APPLICANT
Biovail Laboratories Inc.
#34 Iturregui Avenue
Carolina, Puerto Rico 00983
4. Patent Exclusivity
The Referenced Listed Drug is Trental[®] Extended-release tablets 400 mg, by Hoechst-Roussel Pharmaceuticals, Inc. The drug is not entitled to a period of marketing exclusivity. It is covered by two U.S. patents that expired on February 2, 1997 and April 3, 1997, respectively.
6. PROPRIETARY NAME 7. NONPROPRIETARY NAME
N/A Pentoxifylline Extended-release Tablets
9. AMENDMENTS AND OTHER DATES:

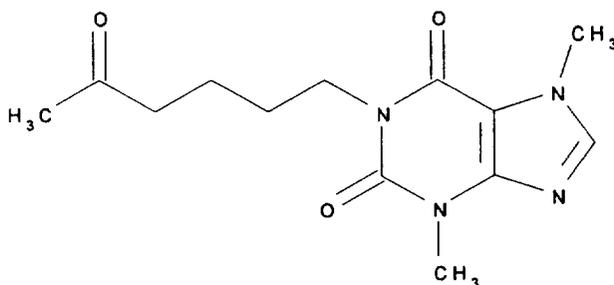
Firm	
Original Submission	12/16/96
Correspondence	2/12/97
Amendment	2/14/97
Amendment (Major)	9/22/97
Amendment (bio)	10/29/97
Amendment	2/12/98
Amendment (bio)	4/9/98
Amendment	6/15/98
FDA	
N/A Letter	2/10/97
Date filed	2/18/97
Label review w/defic.	4/3/97
Chemistry def. Letter	7/31/97
Bio def. Letter	10/14/97
Chem & label def. Fax	1/22/98
Methods acceptable	2/28/98
Bio review acceptable	4/28/98
10. PHARMACOLOGICAL CATEGORY Vasodilator
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM 14. POTENCY
Ext. release tablet 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)-1H-purine-2,6-dione.
CAS [6493-05-6]

17. COMMENTS

Label review satisfactory dated 6/24/98.

EER acceptable dated 7/1/97 and 2/18/98.

Method verification results are acceptable.

Bio review satisfactory.

Firm withdrew the additional two new sources for NDS.

18. CONCLUSIONS AND RECOMMENDATIONS

No outstanding chemistry issues; ANDA can be approved!

19. REVIEWER

Radhika Rajagopalan Ph.D.

DATE COMPLETED

5/15/98

DIVISION APPROVAL SUMMARY

ANDA #: 75-028 DRUG PRODUCT: Pentoxifylline Extended-release Tablets

FIRM: Biovail Laboratories, Inc.

DOSAGE: Extended-release Tablets

STRENGTH: 400 mg

cGMP STATEMENT/EIR UPDATE STATUS:

cGMP: GMP Certification is enclosed. (Page 8442).

EER: Acceptable dated 7/1/97 and 2/18/98.

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:

On 4/28/98 the Division of Bioequivalence issued a letter with dissolution specifications to the firm. The recommended specifications are already in place.

METHODS VALIDATION (Including dosage form description):

Drug substance and drug product are verified by the field labs and found satisfactory. Results filed in volume 1.1.

STABILITY(Conditions, Containers, methods): The product will be distributed in 100 count only.

Evaluation of stability indicating methods: Satisfactory

Stability Assays

Test	Specification
Appearance	White, oblong compressed tablet with 'BVF' on one side and '0117' on the other
Assay	%
Impurities	
Theobromine	NMT %
Other individual	NMT %
Total	NMT %
Dissolution	1 hour NMT % 8 hours NMT % 24 hours NLT %
Moisture content	NMT %

LABELING REVIEW STATUS: Satisfactory. See review dated 6/23/98.

STERILIZATION VALIDATION (If Applicable): Not applicable for this product.

BATCH SIZES:

BIO BATCH: Supplier:

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)

Stability batch is the same as the bio-batch

PROPOSED PRODUCTION BATCH

is the proposed production batch size.

Process is the same as the demonstration batch.

COMMENTS: Approvable

CHEMISTRY REVIEWER:

Radhika Rajagopalan, Ph.D.

DATE:

May 15, 1998

*Remained on extended
leave; letter needs to
issue @ Yammie 7/8/98*

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75028

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #75-028 SPONSOR: Biovail Corporation International
Drug: Pentoxifylline
DOSAGE FORM: Extended-Release Tablets
STRENGTH: 400 mg
TYPE OF STUDIES: Single-dose(Fasting, Non-fasting), Multiple-dose
CLINICAL SITE: Biovail Corporation International
ANALYTICAL SITE:

STUDIES SUMMARY:

The single-dose and multiple-dose bioequivalence studies conducted under fasting conditions, and single-dose food effect study have been found acceptable by the Division of Bioequivalence.

DISSOLUTION:

The dissolution testing has been found acceptable.

PRIMARY REVIEWER: F. Nouravarsani BRANCH: III

SIGNATURE: / S / DATE: 4/27/1998

Acting Team Leader: M. Makary BRANCH: III

SIGNATURE: / S / DATE: 4/27/98

DIRECTOR: Dale P. Conner
DIVISION OF BIOEQUIVALENCE:

SIGNATURE: / S / DATE: 4/28/98

DIRECTOR: Doug Sporn
OFFICE OF GENERIC DRUGS:

SIGNATURE: _____ DATE: _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-028 APPLICANT: Biovail Corporation International

DRUG PRODUCT: Pentoxifylline Extended-Release Tablets, 400 mg

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

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

The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 Apparatus 2 (paddle) at 50 rpm. The test product should meet the following tentative specifications:

<u>Time, hr</u>	<u>Amount Released</u>
1 hour	Not More Than %
8 hours	%
24 hours	Not Less Than %

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

Sincerely yours,

/S/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-028 APPLICANT: Biovail Corporation International

DRUG PRODUCT: Pentoxifylline Extended-Release Tablets, 400 mg

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Sincerely yours,



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

Pentoxifylline	Biovail Corporation International
Extended-Release Tablets	Ontario, Canada
400 mg	Submission Dates:
ANDA #75-028	October 29, 1997
Reviewer: F. Nouravarsani	April 09, 1998
75028SDA.097	

REVIEW OF AMENDMENTS AND RECOMMENDATIONS FOR APPROVAL

Biovail Corporation International had previously submitted three bioequivalence studies (two single-dose studies conducted under fasting and nonfasting conditions, and one multiple-dose study conducted under fasting conditions) and dissolution testing on its test product, Pentoxifylline Extended-Release Tablets, 400 mg and the listed reference product, Trental, 400 mg Pentoxifylline Extended-Release Tablets manufactured by Hoechst Marion Roussel Pharmaceuticals, Inc. in USA (NDA #18631, August 30, 1984).

The firm has responded to the deficiencies of the above studies as follows:

Deficiency #1:

It was stated that, results from rejected batches, if any, were not included in the report. The rejected runs (if any) and the reasons for their rejection were required.

Response to Deficiency #1:

The firm responded that there was one rejected run for study #1775-1. Run FKR-29 was rejected for metabolite V [1-(3-Carboxypropyl)-3,7-Dimethylxanthine], because of "unacceptable deviation of both QC samples". The samples were re-analyzed on run FKR-39. There were no rejected runs for study #1773-1 and #1774-1.

Reviewer Comment:

Results from the rejected run FKR-29 were not submitted for review. The firm was contacted by phone call from the DBE to submit the results of this run.

The firm submitted results of the rejected run on April 09, 1998. Both high Quality Control samples deviated more than % from the nominal concentration.

The firm's response is acceptable.

Deficiency #2:

The Y-scale for the Semi-log Plots was not correct.

Response to Deficiency #2:

The firm responded that "After careful review of the reports, the semi-logarithmic plots for the fasting study (Study #1773-1) and the food-effect study (Study #1775-1) were found to be correct. Typically, the y-scale in a semi-log plot is presented as a logarithmic scale ranging from 1 to 100. Similarly, the semi-log plots in both Study #1773-1 and Study #1775-1 had logarithmic y-scales. However, the ranges of the y-scale in these plots were more specific and related to the study data. For example, in Study #1773-1, the y-scale of the mean semi-log plot ranged from 0.125 to 64.000, with equal tick intervals, and with values doubling per major tick". The firm has further stated that "the semi-log plots for both studies were drawn so that the details of the distribution of the data points for both studies could be seen graphically". A copy of the plot was attached (Attachment 1).

Reviewer Comment:

The firm's explanation is acceptable.

Deficiency #3:

In the Multiple-Dose Study, the curve code FKQ41 was missing from the tables summarizing the quality controls' values and standard concentrations. The firm was requested to clarify.

Response to Deficiency #3:

The firm responded that Curve FKQ-41 was re-injected on Curve FKQ-43 due to system problems.

Reviewer Comment:

The response is acceptable.

Deficiency #4:

The ranges and coefficient of variations (CV%) for all dissolution testing data for each medium were requested to be submitted for both test and reference products at each time point; a dissolution testing method was requested to be suggested; and tentative specifications to be proposed.

Response to Deficiency #4:

The firm submitted mean, ranges, and standard deviation (SD) for the dissolution testing data using media of phosphate buffer solutions pH 1.5, 4.5, 6.5, and 7.5 (Table 1A-D) and water (Table 2). The method conditions were as follows:

Volume: 900 mL

Apparatus: paddle

Stirring Speed: 50 rpm

Sampling Times: 1, 4, 8, 12, 18, and 24 hours.

The proposed tentative Specifications using water as the medium are as follows:

<u>Time, hr</u>	<u>% Drug Release</u>
1	Not More Than %
8	%
24	Not Less Than %

Reviewer Comments:

a. The percentages of Coefficient of Variations (CV%) were calculated by the reviewer (Table 1A-D) and (Table 2).

b. Results of the dissolution testing in buffer solutions show similarity between the test and reference products (Table 1A-D)

c. Results of the mean and individual data demonstrate that

release of the drug is similar in buffer solutions of pH 1.3 to pH 7.5.

d. The mean and individual data points at pH 1.5, 4.5, 6.5, and 7.5 show more than 80% release for both, the test and reference products at 24 hours (Table 1A-D).

e. Results of the dissolution testing in water show similarity between the test and reference products (Table 2).

f. The mean and individual data points for water show more than 80% release for the test product at 24 hours, and for the reference product at 18 hours (Table 2).

g. The percentages of the labeled amount of Pentoxifylline released in water at 1, 8, and 24 hours fall in the USP "Acceptance Table 1" under Drug Release <724>.

h. The test and reference products used in the dissolution testing and bio-studies were from the same bulk lot #96H020 (test product), and lot 0780446 (reference product). The manufacturing date for the test product was August 1996. The expiration date for the reference product was February 1998. The dissolution testing was conducted prior to its expiration.

i. The response is acceptable.

DEFICIENCY OF THE CURRENT SUBMISSIONS: None.

RECOMMENDATIONS:

1. The fasting single-dose, fasting multiple-dose, and nonfasting single-dose bioequivalence studies conducted by Biovail Corporation International on its Pentoxifylline Extended-Release Tablets, 400 mg, lot #96H023 (Bulk lot #96H020) comparing it to Trental Extended-Release Tablets, 400 mg, lot #0780446 have been found acceptable by the Division of Bioequivalence.

The studies demonstrate that Biovail's Pentoxifylline Extended-Release Tablets, 400 mg is bioequivalent to the reference product, Trental, 400 mg Pentoxifylline Extended-Release Tablets manufactured by Hoechst Marion Roussel Pharmaceuticals, Inc.

2. The dissolution testings conducted by Biovail Corporation International on its Pentoxifylline Extended-Release Tablets, 400 mg (Bulk lot #96H020) have been found acceptable by the Division of Bioequivalence.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following tentative specifications:

<u>Time, hr</u>	<u>Amount Released</u>
1 hour	Not More Than %
8 hours	%
24 hours	Not Less Than %

4. From the bioequivalence point of view the firm has met the requirements of in vivo bioequivalency and in vitro dissolution testing.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED MMAKARY
FT INITIALED MMAKARY

/S/

Concur:

/S/

Date: 4/28/98

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

FNouravarsani/04-22-98/75028SDA.097

CC: ANDA #75-028 (Original, Duplicate), HFD-650 (Director),
HFD-658 (Nouravarsani), Drug File, Division File

Table 1: In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline Extended-Release Tablets

Dose Strength: 400 mg

ANDA: #75-028

Firm: Biovail Corporation International

Submission Date: October, 29, 1997

I. Conditions for Dissolution Testing:USP XXIII Basket Paddle X RPM 50 No. Units Tested 12Medium: Phosphate buffer pH 1.5, 4.5, 6.5, and 7.5 at 37° C Volume: 900 mLReference Drug: TrentalAssay Methodology: II. Results of In Vitro Dissolution Testing:

A: pH = 1.5

Sampling Times	Test Product:	Reference Product:
hr	Lot#96H020 (bulk)	Lot #0780446
	Strength (mg) <u>400</u>	Strength (mg) <u>400</u>

	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>13.0</u>	<u> </u>	<u>(4.7)</u>	<u>13.0</u>	<u> </u>	<u>(1.2)</u>
<u>4</u>	<u>31.0</u>	<u> </u>	<u>(4.6)</u>	<u>31.0</u>	<u> </u>	<u>(2.0)</u>
<u>8</u>	<u>50.0</u>	<u> </u>	<u>(3.8)</u>	<u>49.0</u>	<u> </u>	<u>(1.8)</u>
<u>12</u>	<u>65.0</u>	<u> </u>	<u>(3.1)</u>	<u>64.0</u>	<u> </u>	<u>(1.4)</u>
<u>18</u>	<u>83.0</u>	<u> </u>	<u>(2.5)</u>	<u>82.0</u>	<u> </u>	<u>(0.95)</u>
<u>24</u>	<u>94.0</u>	<u> </u>	<u>(2.1)</u>	<u>93.0</u>	<u> </u>	<u>(0.76)</u>

B: pH = 4.5

Sampling Times hr	Test Product: Lot#96H020 Strength (mg) <u>400</u>			Reference Product: Lot #0780446 Strength (mg) <u>400</u>		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>11.0</u>	-	(14.0)	<u>12.0</u>	-	(14.7)
<u>4</u>	<u>27.0</u>	-	(8.0)	<u>28.0</u>	-	(6.8)
<u>8</u>	<u>43.0</u>	-	(5.9)	<u>44.0</u>	-	(4.7)
<u>12</u>	<u>56.0</u>	-	(4.7)	<u>57.0</u>	-	(3.6)
<u>18</u>	<u>73.0</u>	-	(3.3)	<u>74.0</u>	-	(2.5)
<u>24</u>	<u>85.0</u>	-	(2.7)	<u>86.0</u>	-	(1.8)

C: pH = 6.5

Sampling Times hr	Test Product: Lot#96H020 Strength (mg) <u>400</u>			Reference Product: Lot #0780446 Strength (mg) <u>400</u>		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>12.0</u>	-	(3.8)	<u>12.0</u>	-	(2.7)
<u>4</u>	<u>29.0</u>	-	(3.4)	<u>30.0</u>	-	(3.2)
<u>8</u>	<u>46.0</u>	-	(3.1)	<u>48.0</u>	-	(2.9)
<u>12</u>	<u>61.0</u>	-	(2.8)	<u>62.0</u>	-	(2.3)
<u>18</u>	<u>79.0</u>	-	(2.3)	<u>80.0</u>	-	(1.7)
<u>24</u>	<u>91.0</u>	-	(2.1)	<u>92.0</u>	-	(1.6)

D: pH = 7.5

Sampling
Times
hrTest Product:
Lot#96H020
Strength (mg) 400Reference Product:
Lot #0780446
Strength (mg) 400

	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>12.0</u>	-	(6.1)	<u>13.0</u>	-	(1.6)
<u>4</u>	<u>29.0</u>	-	(4.1)	<u>30.0</u>	-	(2.8)
<u>8</u>	<u>46.0</u>	-	(3.4)	<u>48.0</u>	-	(2.2)
<u>12</u>	<u>61.0</u>	-	(2.6)	<u>63.0</u>	-	(1.6)
<u>18</u>	<u>78.0</u>	-	(1.9)	<u>80.0</u>	-	(1.1)
<u>24</u>	<u>90.0</u>	-	(1.7)	<u>92.0</u>	-	(0.89)

Table 2: In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline Extended-Release Tablets

Dose Strength: 400 mg

ANDA: #75-028

Firm: Biovail Corporation International

Submission Date: October 29, 1997

I. Conditions for Dissolution Testing:USP XXIII Basket Paddle X RPM 50 No. Units Tested 12Medium: Water at 37° C Volume: 900 mLReference Drug: Trental

Assay Methodology: _____

Proposed Specifications: 1 hr: NMT %

8 hr: %

24 hr: NLT %

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product:	Reference Product:
hr	Lot#96H020	Lot #0780446
	Strength (mg) <u>400</u>	Strength (mg) <u>400</u>

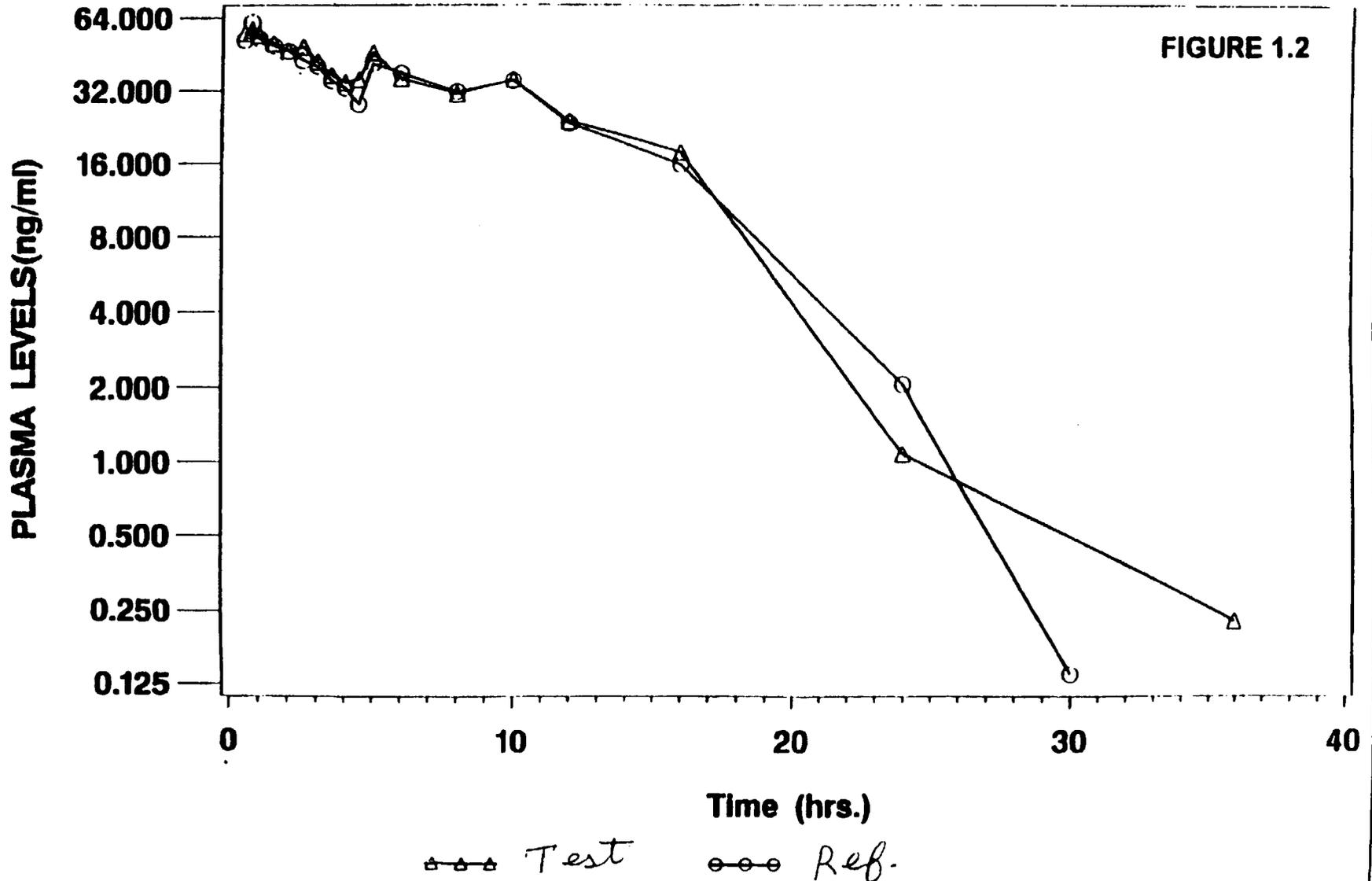
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>11.0</u>	<u> </u>	(11.7)	<u>13.0</u>	<u> </u>	(2.1)
<u>4</u>	<u>30.0</u>	<u> </u>	(5.1)	<u>32.0</u>	<u> </u>	(2.7)
<u>8</u>	<u>49.0</u>	<u> </u>	(4.2)	<u>51.0</u>	<u> </u>	(2.4)
<u>12</u>	<u>64.0</u>	<u> </u>	(3.6)	<u>66.0</u>	<u> </u>	(1.8)
<u>18</u>	<u>82.0</u>	<u> </u>	(2.9)	<u>84.0</u>	<u> </u>	(1.4)
<u>24</u>	<u>93.0</u>	<u> </u>	(2.6)	<u>95.0</u>	<u> </u>	(1.0)

Attachment 1:

SEMI LOG MEAN PLASMA PENTOXIFYLLINE CONCENTRATIONS

STUDY # (1773-1)

FIGURE 1.2



OCT - 2 1997

1

Pentoxifylline
Extended-Release Tablets
400 mg
ANDA #75-028
Reviewer: F. Nouravarsani
75028 SFD.D96

Biovail Corporation International
Toronto, Ontario, Canada
Submission Date:
December 16, 1996

Review of a Single Dose, Fasting Bioequivalence Study and
Dissolution Testing

INTRODUCTION:

As part of the requirements for demonstration of the bioequivalency of the test and reference products, Biovail Corporation International submitted a single dose bioequivalence study conducted under fasting conditions on its test product, Pentoxifylline Extended-Release Tablets, 400 mg and the listed reference product, Trental, 400 mg Pentoxifylline Extended-Release Tablets manufactured by Hoechst Marion Roussel Pharmaceuticals, Inc. in USA (NDA #18631, August 30, 1984).

Pentoxifylline and its metabolites improve the properties of blood flow by decreasing its viscosity. Following administration of 400 mg Extended-Release Tablets of Trental, peak plasma concentrations of pentoxifylline and its metabolites occur within 2 to 4 hours, and remain constant over an extended time (PDR, 1997).

Pentoxifylline is a water soluble compound. Pentoxifylline is almost completely absorbed following oral administration of its aqueous solution. Various first-pass metabolites appear in plasma very soon following the dose. The major metabolites are 1-[5-hydroxyhexyl]-3,7-dimethylxanthine (metabolite I) and 1-[3-carboxypropyl]-3,7-dimethylxanthine (metabolite V). The plasma levels of these metabolites are 5 and 8 times higher, respectively, than pentoxifylline. The pharmacokinetics of pentoxifylline and 1-[5-hydroxyhexyl]-3,7-dimethylxanthine (metabolite I) were found to be non-linear following administration of 100 and 400 mg oral doses of aqueous solutions of pentoxifylline. The elimination kinetics of 1-[3-carboxypropyl]-3,7-dimethylxanthine (metabolite V) are not dose-related (PDR, 1997). Metabolite I, 1-[5-hydroxyhexyl]-3,7-dimethylxanthine is formed by a reversible reduction pathway of pentoxifylline (Division of Bioequivalence "GUIDANCE" dated December 22, 1995).

The Trental, 400 mg Extended-Release Tablets dosage is usually one

tablet three times per day administered with a meal (PDR, 1997).

OBJECTIVES:

1. Determine the bioequivalency of a single dose of the test product, Pentoxifylline Extended-Release Tablets, 400 mg to a single dose of the reference product, Trental, 400 mg Extended-Release Tablets under fasting conditions.

2. Determine the dissolution of the test and reference products.

BIOEQUIVALENCE STUDY:

Sponsor: Biovail Corporation International, Ontario, Canada

Manufacturer: Biovail Corporation International

Clinical and Statistical Facility: Biovail Corporation International, Toronto, Ontario, Canada

Medical Director and Principal Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.

Analytical Facility:

Study Design:

A single dose of the test and reference products, each was administered randomly to healthy male volunteers in a two - way crossover study design under fasting conditions (study #1773-1).

Treatments:

Treatment A (test product): A single dose of Pentoxifylline Extended-Release Tablets, 400 mg, Bulk lot #96H020 (Packaged lot #96H023), batch size of Tablets, manufacturing date: August 1996.

Treatment B (reference product): A single dose of Trental, Pentoxifylline Extended-Release Tablets, 400 mg, lot #0780446, expiration date: February 1998.

Clinical Study Dosing Dates:

Phase I: September 14, 1996

Phase II: September 21, 1996

Washout period: one week

Subjects:

Fourty-seven (47) healthy, non-smokers, male volunteers were

enrolled and completed the study. The range of subjects' age, weight, and height are summarized as follows:

Age: 19-45 years; Weight: 142-233 pounds; Height: 63-78 inches

Housing, Food and Fluid Intake:

The subjects were housed from evening before the dosing until 36 hours after the dose of each period. The subjects fasted overnight prior to the dosing and 4.5 hours after the dose. Standard meals were served for both periods. The subjects were allowed to drink water ad lib, except within one hour of the dose administration. However, the dose was taken with 240 mL water.

Blood Samples:

A total of twenty (20) blood samples, 10 mL each, were collected for each phase at pre-dose, and at 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 30.0, and 36.0 hours post-dose.

Analytical Procedures:

Lower Limit of Quantitation:

Pentoxifylline: 4.97 ng/mL
1-(3-Carboxypropyl)-3,7-Dimethylxanthine (CPDX): 14.89 ng/mL
5-Hydroxypentoxifylline: 10.02 ng/mL

Linearity:

linear regression analysis, weighting factor: 1/Concentration

Specificity:

There were no interferences from the analytes and the internal standard.

Internal Standard: 1-(5-Carboxypentyl)-3,7-Dimethylxanthine

Accuracy:**Pentoxifylline:**

(a) from the standard samples, concentration range of
ng/mL, Interday: %

(b) from the quality control samples, concentration range of
ng/mL, Interday: %

1-(3-Carboxypropyl)-3,7-Dimethylxanthine (CPDX):

(a) from the standard samples, concentration range of
ng/mL, Interday: %

(b) from the quality control samples, concentration range of
ng/mL, Interday: %

5-Hydroxypentoxifylline:

(a) from the standard samples, concentration range of
ng/mL, Interday: %

(b) from the quality control samples, concentration range of
ng/mL, Interday: %

Precision, CV%:**Pentoxifylline:**

(a) from the standard samples, concentration range of
ng/mL, Interday: %

(b) from the quality control samples, concentration range of
ng/mL, Interday: %

1-(3-Carboxypropyl)-3,7-Dimethylxanthine (CPDX):

(a) from the standard samples, concentration range of
ng/mL, Interday: %

(b) from the quality control samples, concentration range of
ng/mL, Interday: %

5-Hydroxypentoxifylline:

(a) from the standard samples, concentration range of
ng/mL, Interday: %

(b) from the quality control samples, concentration range of
ng/mL, Interday: %

Stability Studies:Frozen Long Term Stability:

The frozen plasma stability study period, 301 days, at -22° C for the analytes covers the length of clinical and analytical study. The study samples were stored at -22° C for a duration of not exceeding 43 days.

Short Term (Benchtop) Stability:

The samples were stable at 22° C for 5.5 hours.

Freeze-Thaw Stability:

The samples were stable after three freeze-thaw cycles.

Autosampler Stability:

The samples were stable at 22° C for 41.5 hours.

Repeated Analysis:Pentoxifylline:

Thirty-one (1.6%) samples were coded D (anomalous sample value), and were reassayed for Pentoxifylline. The repeated value (median) of one sample (subject #8, period 1, test) is C(Max). The repeated duplicate values of 45.04 ng/mL and 45.45 ng/mL are very similar to the original assayed value of 44.89 ng/mL.

Three (0.2%) samples were coded "B" (lost in processing). These samples were assayed. One sample (0.75 hour, subject 27, period 1, ref.) Was C(Max).

5-Hydroxypentoxifylline:

Thirty-two samples (1.7%) were coded D (anomalous sample value), and were reassayed. The median values were reported. None of these samples was C(Max).

Three (0.2%) samples were coded "B" (lost in processing). These samples were assayed.

Three (0.2%) samples were coded "G" (High\Low standard missing from the regression). They were reassayed.

CPDX:

Thirty-one (1.6%) samples were coded D (anomalous sample value), and were reassayed. The median values were reported. None of

these samples was C(Max).

Three (0.2%) samples were coded "B" (lost in processing). These samples were assayed. One sample (0.75 hour, subject #27, period 1, ref. Product) was C(Max).

Statistical Analysis:

The data from Pentoxifylline, 1-(3-Carboxypropyl)-3,7-dimethylxanthine (CPDX), and 5-OH-Pentoxifylline were analyzed using SAS-GLM procedure. The two one sided t-test procedure (90% confidence intervals) was used to compare the ln-transformed pharmacokinetic parameters of AUC(0-T), AUC(0-Inf), and C(Max) obtained from the test and the reference products. The ratios of the geometric means were also calculated for the parameters.

Results:

Mean plasma concentrations of Pentoxifylline, CPDX, and 5-OH-Pentoxifylline obtained from the test and reference products are summarized in Tables 1-3. Plots of the mean plasma concentrations of Pentoxifylline, CPDX, and 5-OH-Pentoxifylline versus time for both, the test and reference products are shown in Figures 1-3. The means of the pharmacokinetic parameters for Pentoxifylline, CPDX, and 5-OH-Pentoxifylline obtained from the test and reference products are compared in Tables 4-6.

Pentoxifylline:

The AUC(0-T) obtained for the test product Pentoxifylline, 551.08 hr*ng/mL is comparable with the one obtained from the reference product, 533.89 hr*ng/mL.

Mean value of 732.15 hr*ng/mL obtained for the test product AUC(0-Inf) is comparable with the one obtained for the reference product, 731.76 hr*ng/mL, respectively.

Mean C(Max) value of 75.78 ng/mL obtained for the test product is also comparable with mean C(Max) value of 75.42 ng/mL obtained for the reference product. Multiple peaks are observed for Pentoxifylline in both the test and reference products data.

The 90% confidence intervals based on Least Squares Means obtained for Pentoxifylline parameters (log-transformed) of AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range of 80 - 125% (Table 4). There is period effect ($\alpha=0.05$) for LnAUC(0-Inf) The reason for this effect was not explained by the firm.

AUC(0-Inf) for Pentoxifylline was not calculated for 8 subjects (#1, 6, 8, 21, 24, 37, 40, and 47) for the test product, and for 11 subjects (#1, 4, 6, 8, 19, 21, 30, 33, 41, 42, and 47) for the reference product.

Fourteen subjects (#5, 11, 14, 15, 23, 25, 26, 29, 30, 31, 32, 33, 43, and 45) showed C(Max) at 0.5 hour, which is the first post dose sample collected for the test product. Thirteen subjects (#2, 7, 9, 10, 11, 13, 14, 17, 21, 24, 25, 42, and 44) showed C(Max) at 0.5 hour for the reference product.

CPDX:

The AUC(0-T) obtained for the test product, CPDX, 5662.6 hr*ng/mL is comparable with the one obtained from the reference product, 5581.5 hr*ng/mL.

Mean value of 6033.5 hr*ng/mL obtained for the test product AUC(0-Inf) is comparable with the one obtained for the reference product, 6268.5 hr*ng/mL, respectively.

Mean C(Max) value of 608.3 ng/mL obtained for the test product is also comparable with the mean C(Max) value of 636.5 ng/mL obtained for the reference product. Multiple peaks are observed for CPDX in both the test and reference products data.

The 90% confidence intervals based on Least Squares Means obtained for parameters (log-transformed) of AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range of 80 - 125% (Table 5). There is treatment effect ($\alpha=0.05$) and sequence effect ($\alpha=0.1$) for LnC(Max). No explanation was given by the firm for these effects.

The AUC(0-Inf) for CPDX could not be calculated for 3 subjects (#5, 17, and 25) for the reference product.

5-OH-Pentoxifylline:

The AUC(0-T) obtained for the test product, 5-OH-Pentoxifylline, 2418.2 hr*ng/mL is comparable with the one obtained from the reference product, 2404.3 hr*ng/mL.

Mean value of 2719.1 hr*ng/mL obtained for the test product AUC(0-Inf) is comparable with the one obtained for the reference product, 2901.3 hr*ng/mL, respectively.

Mean C(Max) value of 249.9 ng/mL obtained for the test product is also comparable with the mean C(Max) value of 249.6 ng/mL obtained

for the reference product. Multiple peaks are observed for 5-OH-Pentoxifylline in both the test and reference products data.

The 90% confidence intervals based on Least Squares Means obtained for 5-OH-Pentoxifylline parameters (log-transformed) of AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range of 80 - 125% (Table 6). There is period effect ($\alpha=0.05$) for LnAUC(0-T). No explanation was given by the firm for this effect.

The AUC(0-Inf) for 5-OH-Pentoxifylline could not be calculated for 3 subjects (#2, 46, and 47) for the test product, and for 4 subjects (#6, 17, 21, and 33) for the reference product.

Adverse Events:

Adverse events were reported during the first period as follows:

<u>Subject</u>	<u>Adverse Event</u>	<u>Product</u>	<u>Probably Drug Related</u>
13	Headache	Ref.	yes
44	Headache	Test	yes
42	Diaphoretic	Ref.	No
	Pallor		No
	Lightheadedness		NO
	Nausea		No
46	Pallor	Test	No
	Diaphoretic		No
	Lightheadedness		No

In-Vitro Studies:

Dissolution Testing:

Dissolution testings were conducted on 12 units of the test and reference products in 900 mL phosphate buffer at pH 1.5, pH 4.5, pH 6.5, pH 7.5, and water using apparatus 2 at 50 rpm. Only mean data were submitted (Tables 7 and 8).

Assay Potency:

Assay potencies of 99.9% and 100.5% of the label claimed were obtained for the test and reference products, respectively. Formulations of the test and reference products are compared in Table 9.

Content Uniformity:

Means (CV%, N) content uniformities of 99.5% (2%, N=10) and 98.0% (2.7%, 10) were obtained for the test and reference products, respectively.

COMMENTS:

1. Fourteen (14) subjects for the test product, and 13 subjects for the reference products showed C(Max) value at 0.5 hr, the first sample collected post dose for Pentoxifylline. The pharmacokinetics parameters were statistically reanalyzed, and 90% CIs and ratios were recalculated by excluding these subjects by the reviewer.

The 90% confidence intervals obtained for the Ln-transformed pharmacokinetic parameters of AUC(0-T), AUC(0-Inf), and C(Max) for Pentoxifylline, CPDX, and 5-OH-Pentoxifylline fall within the required range of 80-125% by including all of the subjects, or excluding subjects with C(Max) at 0.5 hr.

2. Bulk lot #96H020 (Packaged lot #96H023), test product, and lot #0780446, reference product, were used for the bioequivalence studies of single dose under fasting and non-fasting conditions, steady-state multiple dose under fasting conditions, and dissolution testing. The test product batch size was units.

3. Multiple peaks are observed for Pentoxifylline, CPDX, and 5-OH-Pentoxifylline for both, the test and reference products. The presence of multiple peaks are apparently due to the reversible metabolism of Pentoxifylline to metabolite I, 5-OH-Pentoxifylline.

4. The AUC(0-Inf) was not calculated for some of the subjects for both, the test and reference products, because of difficulty to calculate the K(Elm). Accurate determination of the K(Elm) is not possible due to apparently reversible metabolism of Pentoxifylline to metabolite I, 5-OH-Pentoxifylline.

5. There is a guidance available for pentoxifylline Extended-Release Tablets, 400 mg in the Division of Bioequivalence (Dec. 22, 1995).

DEFICIENCIES:

1. The firm should be informed that Y-scale for the Semi-log Plots are not correct.

2. The firm has stated that "results from rejected batches, if any, are not included in the report".

The rejected runs, if any, and the reason(s) for rejecting should be submitted by the firm.

3. The ranges and coefficient of variations (CV%) for the dissolution testing data for each medium should be submitted for both, the test and reference products. A dissolution testing method and specifications should be proposed.

RECOMMENDATIONS:

1. The single dose bioequivalence study conducted under fasting conditions by Biovail Corporation International on its Pentoxifylline Extended-Release Tablets, 400 mg, lot #96H023 (Bulk lot #96H020) comparing it to Trental Extended Release Tablets, 400 mg, lot #0780446 has been found incomplete by the Division of Bioequivalence.

2. The dissolution testing conducted by Biovail Corporation International on its Pentoxifylline Extended-Release Tablets, 400 mg (Bulk lot #96H020) has been found incomplete.

The firm should be informed of the deficiencies 1-3, and recommendations.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/

8/29/97

Concur: _____

Date: *10/2/97*

f Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/08-28-97/75028SFD.D96

CC: ANDA #75-028 (Original, duplicate), HFD-650 (Director), HFD-658 (Nouravarsani), Drug File, Division File.

Table 1

Mean (CV%) Plasma Concentrations (ng/mL) of Pentoxifylline, N=47:

<u>Time, hr</u>	<u>Test Product</u>	<u>Ref. Product</u>
0.00	0.00 (--)	0.00 (--)
0.50	55.04 (69)	51.50 (69)
0.75	56.57 (49)	61.14 (55)
1.00	54.03 (56)	52.28 (56)
1.50	50.01 (63)	48.77 (52)
2.00	46.51 (67)	46.33 (70)
2.50	48.18 (69)	42.44 (71)
3.00	41.96 (61)	40.15 (69)
3.50	36.95 (57)	35.06 (79)
4.00	34.41 (52)	32.59 (79)
4.50	35.38 (76)	27.91 (88)
5.00	45.76 (72)	41.05 (63)
6.00	35.77 (78)	37.65 (77)
8.00	30.89 (80)	31.50 (80)
10.00	35.39 (70)	35.05 (81)
12.00	23.88 (89)	23.30 (82)
16.00	17.70 (88)	15.71 (74)
24.00	1.07 (304)	02.04 (207)
30.00	0.00 (--)	0.14 (686)
36.00	0.22 (686)	0.00 (0.0)

Table 2

Mean (CV%) Plasma Concentrations of CPDX (ng/mL), N=47:

<u>Time, hr</u>	<u>Test Product</u>	<u>Ref. Product</u>
0.00	0.00 (--)	0.00 (--)
0.50	295.8 (37)	305.2 (41)
0.75	456.9 (27)	488.5 (29)
1.00	518.9 (24)	551.0 (26)
1.50	545.6 (23)	567.9 (24)
2.00	534.0 (26)	547.2 (22)
2.50	532.3 (27)	516.3 (25)
3.00	503.3 (28)	479.2 (28)
3.50	464.0 (29)	439.4 (28)
4.00	429.8 (31)	411.9 (30)
4.50	420.0 (34)	378.4 (33)
5.00	404.1 (31)	367.9 (32)
6.00	338.8 (32)	343.8 (30)
8.00	263.8 (38)	264.8 (35)
10.00	242.6 (40)	241.4 (32)
12.00	200.2 (49)	198.4 (43)
16.00	165.2 (55)	152.9 (50)
24.00	34.6 (108)	050.4 (116)
30.00	4.47 (415)	2.61 (348)
36.00	0.42 (686)	0.00 (---)

Table 3

Mean (CV%) Plasma Concentrations (ng/mL) of 5-OH-Pentoxifylline,
N=47:

<u>Time, hr</u>	<u>Test Product</u>	<u>Ref. Product</u>
0.00	0.00 (--)	0.00 (--)
0.50	83.29 (77)	82.53 (78)
0.75	135.8 (57)	144.4 (61)
1.00	169.8 (52)	175.7 (57)
1.50	202.5 (51)	208.2 (58)
2.00	221.1 (54)	225.2 (60)
2.50	230.1 (54)	227.9 (70)
3.00	220.6 (51)	220.6 (73)
3.50	206.0 (53)	207.0 (76)
4.00	191.8 (51)	193.9 (78)
4.50	186.7 (52)	179.6 (79)
5.00	180.4 (56)	174.6 (73)
6.00	151.0 (65)	156.1 (71)
8.00	119.3 (75)	123.8 (76)
10.00	111.9 (74)	114.3 (75)
12.00	99.9 (81)	101.2 (89)
16.00	74.3 (79)	67.8 (81)
24.00	12.1 (117)	15.2 (104)
30.00	0.93 (547)	0.44 (686)
36.00	0.00 (--)	0.00 (--)

Table 4

Arithmetic Mean (CV%), Ratio, and 90% CI for Pentoxifylline Pharmacokinetic Parameters (Single Dose, Fasting) Obtained from the Test and Reference Products, N=47:

<u>Parameters</u>	<u>Test Product</u>	<u>Ref. Product</u>	<u>Ratio*</u>	<u>90% CI**</u>
AUC (0-T) hr*ng/mL	551.08 (63.9)	533.89 (62.3)	101.5%	93.7-109.9
AUC (0-Inf) hr*ng/mL	732.15 (61.9)	731.76 (57.5)	99.01%	88.8-110.5
C (Max) ng/mL	75.78 (57.4)	75.42 (48.3)	97.58%	88.5-107.6
T (Max) hr	1.94 (115)	1.69 (120)		
K (Elm) 1/hr	0.170 (58.6)	0.166 (94.7)		
T (1/2) hr	6.46 (90.8)	7.67 (76.0)		

* = using geometric means

** = using log-transformed data

90% CI and ratio for 23 subjects (excluding subjects with C(Max) at 0.5 hour):

<u>Parameters</u>	<u>90% CI (a)</u>	<u>Ratio (b)</u>
AUC (0-T) hr*ng/mL	91.83% - 120.53%	105%
AUC (0-Inf) hr*ng/mL	84.60% - 112.34%	97%
C (Max) ng/mL	82.53% - 111.77%	96%

a: using log-transformed data

b: using geometric means

Table 5

Arithmetic Mean (CV%), Ratio, and 90% CI for CPDX Pharmacokinetic Parameters (Single Dose, Fasting) Obtained from the Test and Reference Products, N=47:

<u>Parameters</u>	<u>Test Product</u>	<u>Ref. Product</u>	<u>Ratio *</u>	<u>90% CI **</u>
AUC(0-T) hr*ng/mL	5662.6 (25.5)	5581.5 (24.7)	101.0%	95.5-106.9
AUC(0-Inf) hr*ng/mL	6033.5 (24.2)	6268.5 (24.2)	96.5%	90.2-103.2
C(Max) ng/mL	608.3 (22.2)	636.5 (19.9)	95.3%	91.8-98.9
T(Max) hr	2.02 (54.5)	1.79 (64.6)		
K(Elm) 1/hr	0.213 (56.5)	0.178 (54.8)		
T(1/2) hr	4.13 (47.4)	5.55 (77.5)		

* = using geometric means

** = using log-transformed data

Table 6

Arithmetic Mean (CV%), Ratio, and 90% CI for 5-OH-Pentoxifylline Pharmacokinetic Parameters (Single Dose, Fasting) Obtained from the Test and Reference Products, N=47:

<u>Parameters</u>	<u>Test Product</u>	<u>Ref. Product</u>	<u>Ratio *</u>	<u>90% CI **</u>
AUC(0-T) hr*ng/mL	2418.2 (62.8)	2404.3 (71.2)	102.2%	96.5-108.3
AUC(0-Inf) hr*ng/mL	2719.1 (54.4)	2901.3 (60.3)	95.94%	88.4-104.2
C(Max) ng/mL	249.9 (50.9)	249.6 (65.6)	105.7%	99.1-112.8
T(Max) hr	2.67 (31.3)	2.44 (48.7)		
K(Elm) 1/hr	0.172 (53.2)	0.150 (61.1)		
T(1/2) hr	5.42 (66.3)	6.27 (56.7)		

* = using geometric means

** = using log-transformed data

Table 7: In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline Extended-Release Tablets

Dose Strength: 400 mg

ANDA: #75-028

Firm: Biovail Corporation International

Submission Date: December 16, 1996

I. Conditions for Dissolution Testing:USP XXIII Basket Paddle X RPM 50 No. Units Tested 12Medium: Phosphate buffer pH 1.5, 4.5, 6.5, and 7.5 at 37° C Volume: 900 mLReference Drug: Trental

Assay Methodology: _____

II. Results of In Vitro Dissolution Testing:

A: pH = 1.5

Sampling Times hr	Test Product: Lot#96H020 (bulk) Strength (mg) <u>400</u>	Reference Product: Lot #0780446 Strength (mg) <u>400</u>
	Mean% Range% (CV%)	Mean% Range% (CV%)
<u>1</u>	<u>13.0</u> - (.....)	<u>13.0</u> - (.....)
<u>4</u>	<u>32.0</u> - (.....)	<u>31.0</u> - (.....)
<u>8</u>	<u>50.0</u> - (.....)	<u>49.0</u> - (.....)
<u>12</u>	<u>66.0</u> - (.....)	<u>64.0</u> - (.....)
<u>18</u>	<u>84.0</u> - (.....)	<u>82.0</u> - (.....)
<u>24</u>	<u>95.0</u> - (.....)	<u>93.0</u> - (.....)

B: pH = 4.5

Sampling Times hr	Test Product: Lot#96H020 Strength (mg) <u>400</u>	Reference Product: Lot #0780446 Strength (mg) <u>400</u>
----------------------	---	--

	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>12.0</u>	-	(.....)	<u>12.0</u>	-	(.....)
<u>4</u>	<u>28.0</u>	-	(.....)	<u>28.0</u>	-	(.....)
<u>8</u>	<u>43.0</u>	-	(.....)	<u>44.0</u>	-	(.....)
<u>12</u>	<u>57.0</u>	-	(.....)	<u>57.0</u>	-	(.....)
<u>18</u>	<u>73.0</u>	-	(.....)	<u>74.0</u>	-	(.....)
<u>24</u>	<u>85.0</u>	-	(.....)	<u>86.0</u>	-	(.....)

C: pH = 6.5

Sampling Times hr	Test Product: Lot#96H020 Strength (mg) <u>400</u>	Reference Product: Lot #0780446 Strength (mg) <u>400</u>
----------------------	---	--

	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>12.0</u>	-	(.....)	<u>12.0</u>	-	(.....)
<u>4</u>	<u>29.0</u>	-	(.....)	<u>30.0</u>	-	(.....)
<u>8</u>	<u>47.0</u>	-	(.....)	<u>48.0</u>	-	(.....)
<u>12</u>	<u>62.0</u>	-	(.....)	<u>62.0</u>	-	(.....)
<u>18</u>	<u>79.0</u>	-	(.....)	<u>80.0</u>	-	(.....)
<u>24</u>	<u>91.0</u>	-	(.....)	<u>92.0</u>	-	(.....)

D: pH = 7.5

Sampling
Times
hrTest Product:
Lot#96H020
Strength (mg) 400Reference Product:
Lot #0780446
Strength (mg) 400

	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>12.0</u>	-	(.....)	<u>13.0</u>	.	-(.....)
<u>4</u>	<u>29.0</u>	-	(.....)	<u>31.0</u>	.	-(.....)
<u>8</u>	<u>46.0</u>	-	(.....)	<u>48.0</u>	.	-(.....)
<u>12</u>	<u>61.0</u>	-	(.....)	<u>63.0</u>	.	-(.....)
<u>18</u>	<u>78.0</u>	-	(.....)	<u>80.0</u>	.	-(.....)
<u>24</u>	<u>90.0</u>	-	(.....)	<u>92.0</u>	.	-(.....)

Table 8: In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline Extended-Release Tablets

Dose Strength: 400 mg

ANDA: #75-028

Firm: Biovail Corporation International

Submission Date: December 16, 1996

I. Conditions for Dissolution Testing:USP XXIII Basket Paddle X RPM 50 No. Units Tested 12Medium: Water at 37° C Volume: 900 mLReference Drug: Trental

Assay Methodology: _____

Proposed Specifications: 1 hr: NMT %
 4 hr: %
 8 hr: %
 12 hr: %
 18 hr: NLT %
 24 hr: NLT %

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product:	Reference Product:
hr	Lot#96H020	Lot #0780446
	Strength (mg) <u>400</u>	Strength (mg) <u>400</u>

	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>1</u>	<u>11.0</u>		- (.....)	<u>13.0</u>		- (.....)
<u>4</u>	<u>30.0</u>		- (.....)	<u>32.0</u>		- (.....)
<u>8</u>	<u>49.0</u>		- (.....)	<u>51.0</u>		- (.....)
<u>12</u>	<u>64.0</u>		- (.....)	<u>67.0</u>		- (.....)
<u>18</u>	<u>82.0</u>		- (.....)	<u>85.0</u>		- (.....)
<u>24</u>	<u>93.0</u>		- (.....)	<u>96.0</u>		- (.....)

Table 9: Formulations Comparison of the Test and Reference products, mg/Tablet:

<u>Ingredients</u>	<u>Test, mg</u>	<u>Ref., mg (a)</u>
Pentoxifylline	400	400
Hydroxyethyl Cellulose		
Povidone		
Talc		
Magnesium Stearate		
Isopropyl Alcohol		
Benzyl Alcohol		
Hydroxypropyl Methylcellulose		
Polyethylene glycol		
Titanium Dioxide		
D&C Red No.27 Aluminum Lake or FD&C Red #3		
other ingredients		

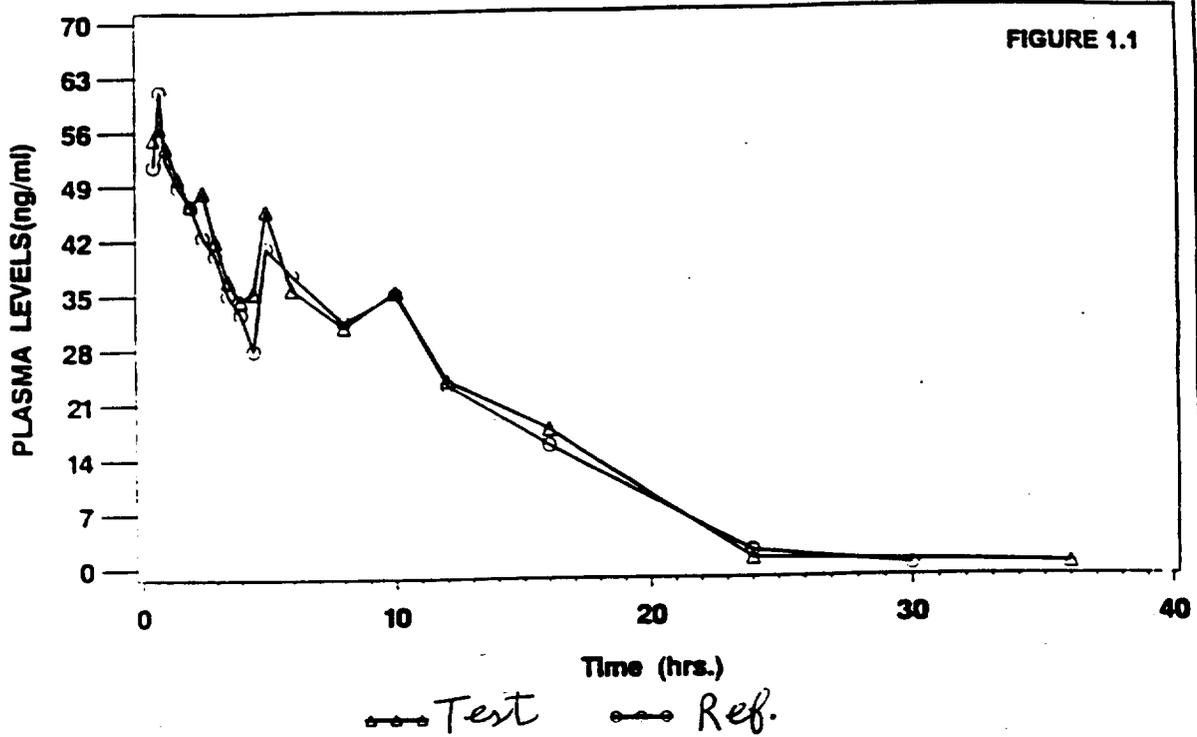
a: From the PDR (1997).

*: Isopropyl Alcohol was evaporated during drying of the wet granulation.

X: Present in the reference product.

Figure 1

MEAN PLASMA PENTOXIFYLLINE CONCENTRATIONS STUDY # (1773-1)



SEMI LOG MEAN PLASMA PENTOXIFYLLINE CONCENTRATIONS STUDY # (1773-1)

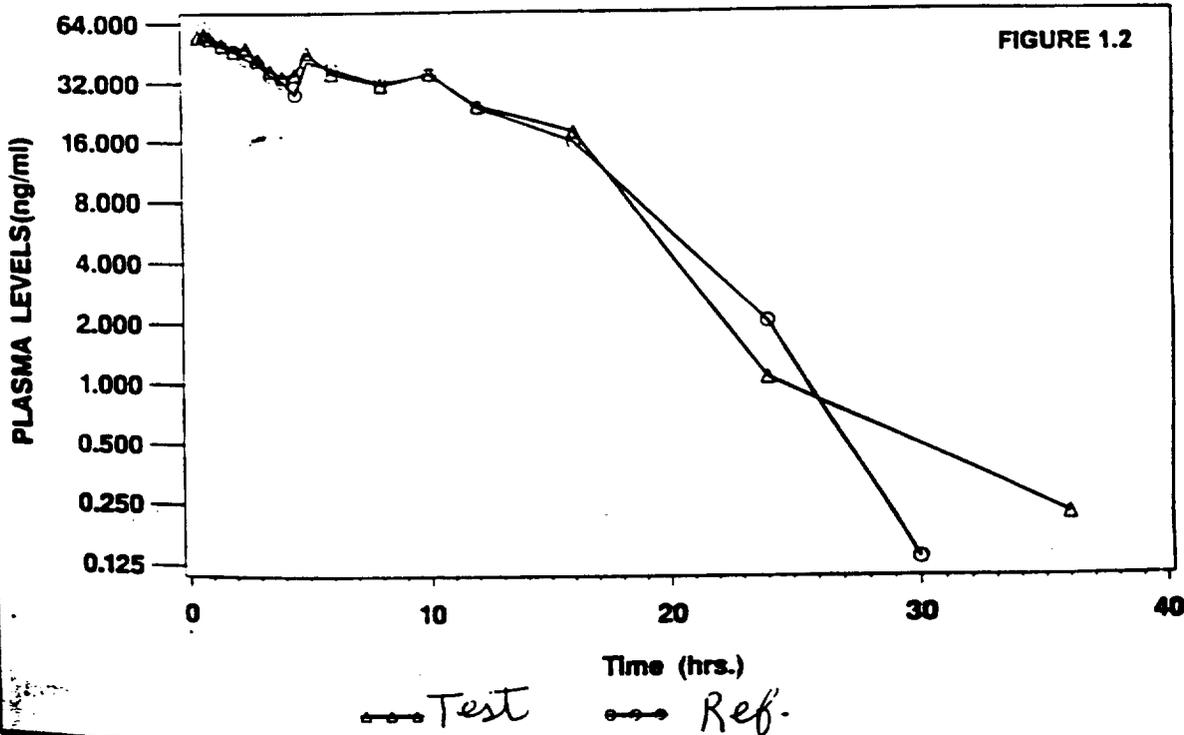


Figure 2

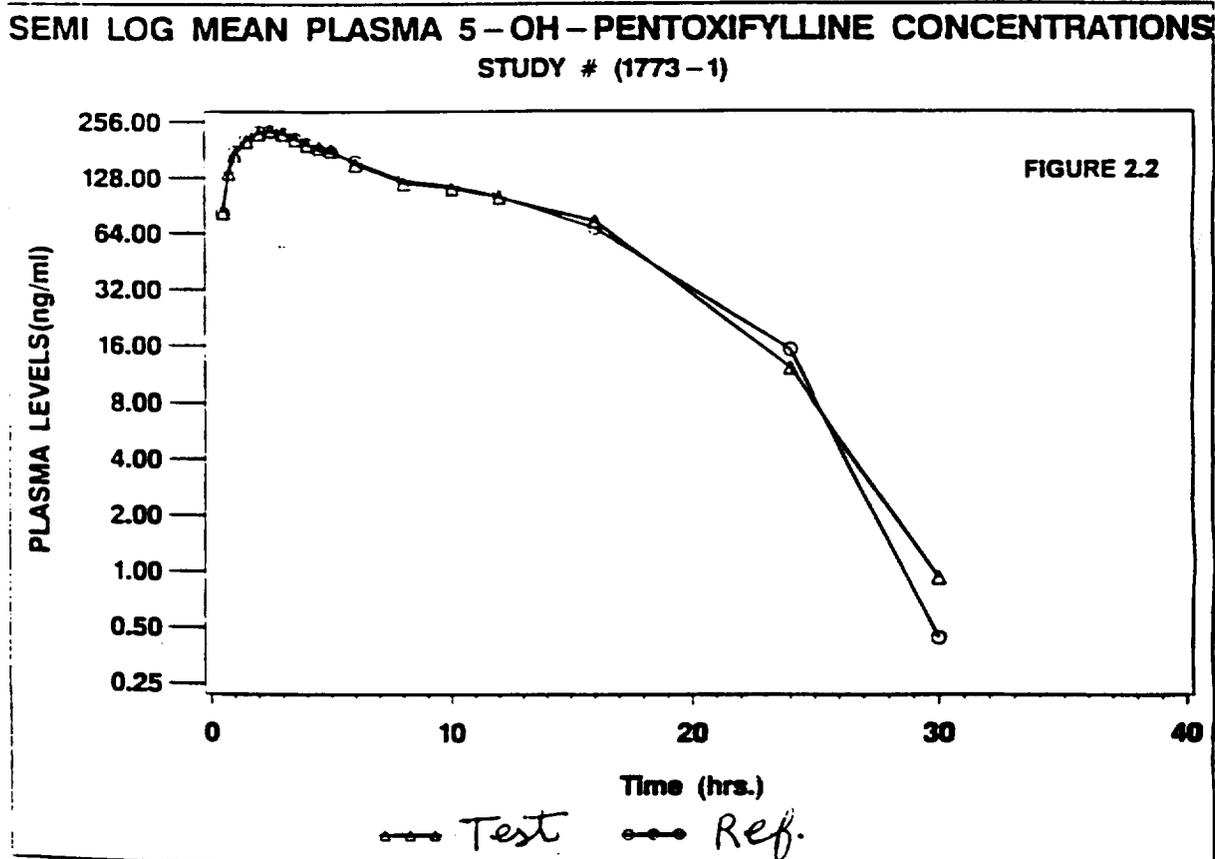
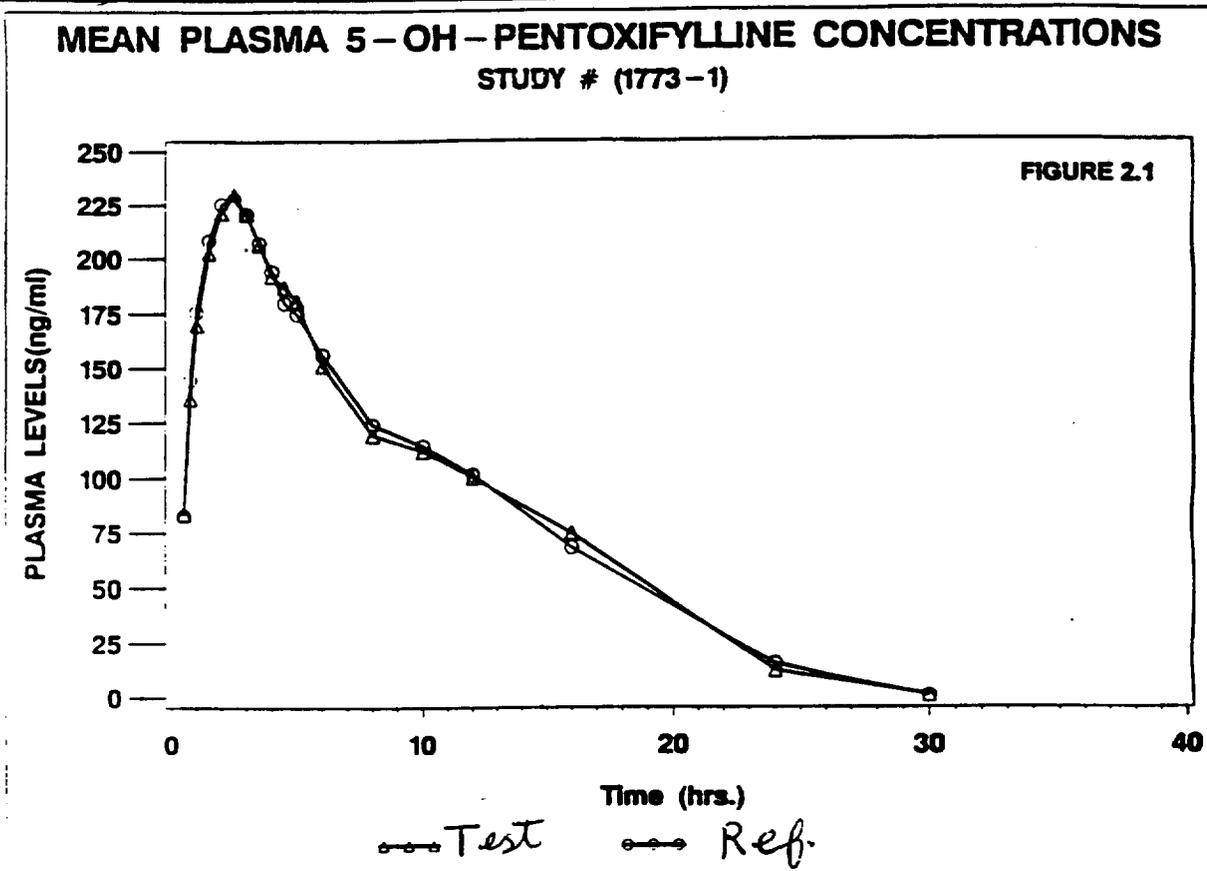
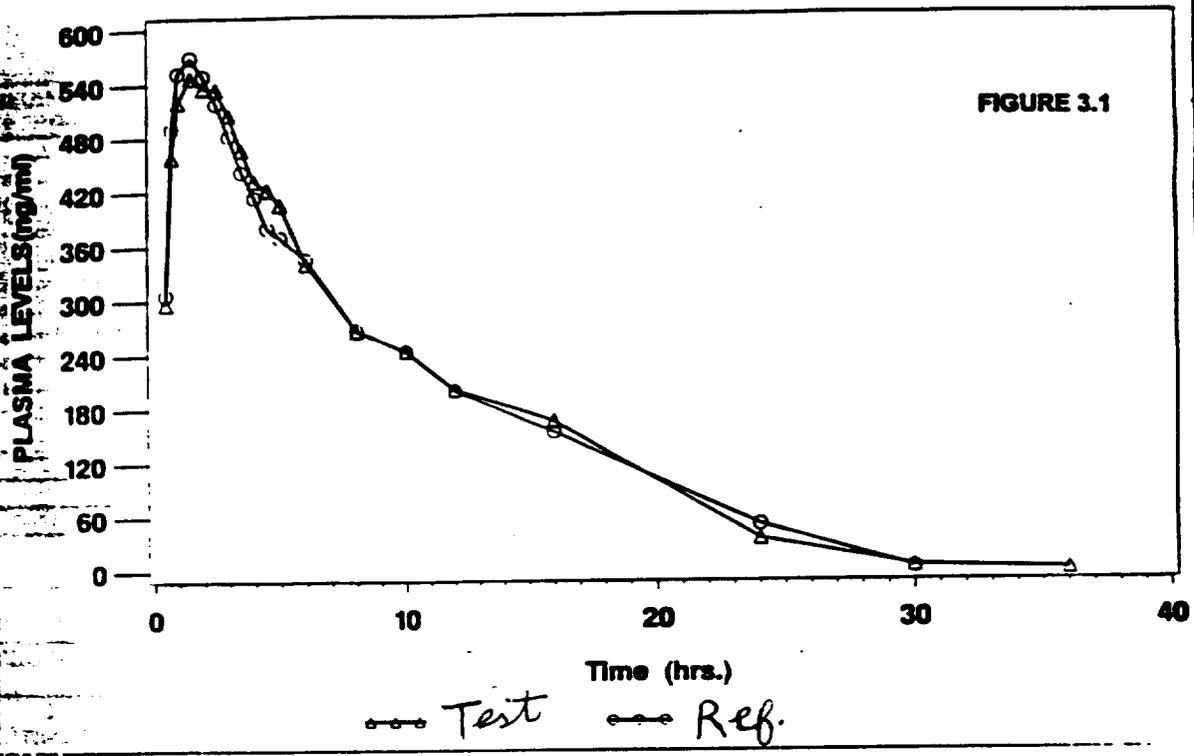
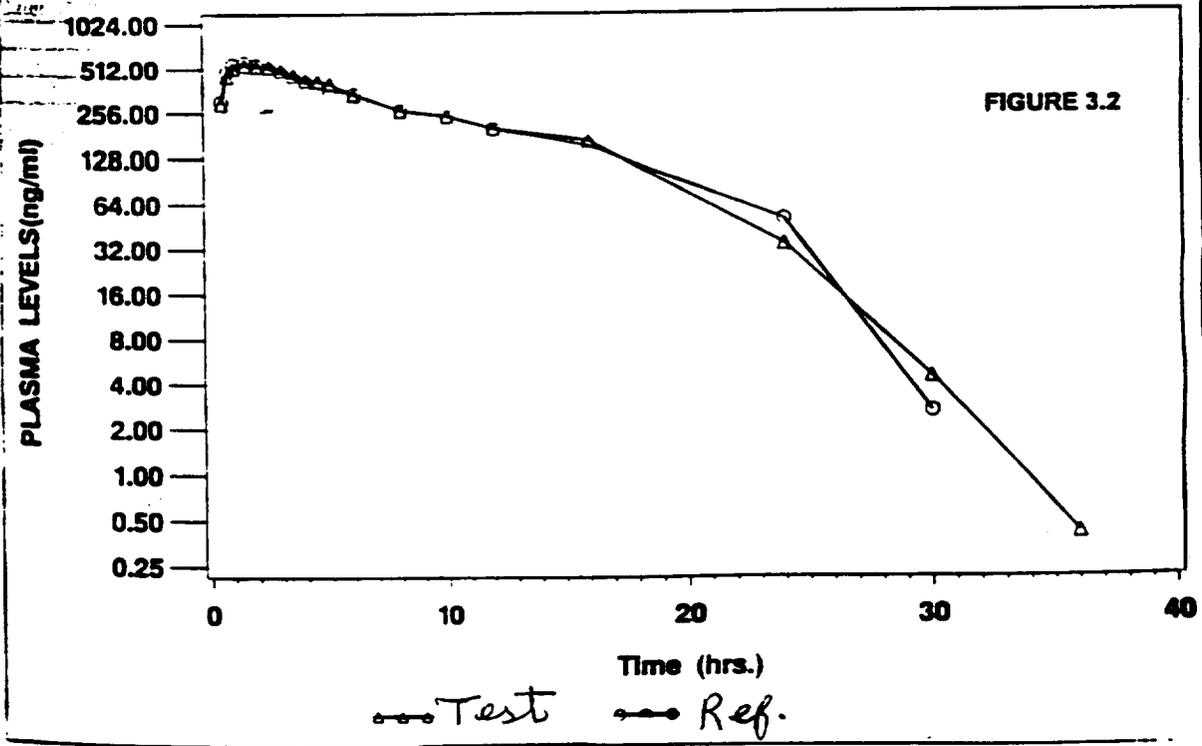


Figure 3

MEAN PLASMA CPDX CONCENTRATIONS
STUDY # (1773-1)



SEMI LOG MEAN PLASMA CPDX CONCENTRATIONS
STUDY # (1773-1)



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75028

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 75-028 Date of Submission: October 29, 1997

Applicant's Name : Biovail Laboratories Inc.

Established Name: Pentoxifylline Extended-release Tablets, 400 mg

LABELING DEFICIENCIES

1. CONTAINER (100's)

Revise your statement of storage temperature to include degrees celcius as seen in the HOW SUPPLIED section of your insert labeling.

2. INSERT

a. Please ensure that the boxed text format, for example, that appearing in the DESCRIPTION section, does not appear in your final printed insert labeling.

b. DESCRIPTION

Revise the line above the structural formula to read:

The structural formula is:

c. ADVERSE REACTIONS

Align column headings such that the text "Pentoxifylline Extended-release Tablets" appears over the first and third columns and "Placebo" appears over the second and fourth columns.

d. OVERDOSAGE

In the first sentence replace "children" with "pediatric patients".

e. HOW SUPPLIED

We encourage inclusion of the "CAUTION: Federal...", statement as seen on your container labels.

Revise your container labels and package insert labeling as described above, then prepare and submit final printed labeling.

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

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

M *1*
/S/ *Sar*

Jerry Phillips //
Director
Division of Labeling and Program Support
Center for Drug Evaluation and Research

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

ANDA Number: 75-028 Date of Submission: December 16, 1996

Applicant's Name : Biovail Laboratories Inc.

Established Name: Pentoxifylline Extended-release Tablets, 400 mg

LABELING DEFICIENCIES

1. CONTAINER (100's)

Your manufactured for/by statement for the USA and foreign company must comply with 21 CFR 201.1(6)(i). The place of business shall include the street address, city, state/country and zip code/mailling code. Please see the citation above for guidance.

2. INSERT

a. DESCRIPTION

- i. The CAS registry number may be deleted.
- ii. The chemical name should read 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione.
- iii. Include the molecular weight - 278.31.
- iv. Include the molecular formula - $C_{13}H_{18}N_4O_3$.
- v. ...isopropyl alcohol in an extended-release... (delete "and").

b. INDICATIONS AND USAGE

- i. First sentence - Pentoxifylline extended-release tablets are indicated...
- ii. Second sentence - Pentoxifylline extended-release tablets can...

c. PRECAUTIONS

- i. Please use "pentoxifylline" rather than "pentoxifylline extended-release" tablet in this section.

- ii. In the fourth sentence of the General subsection and the second sentence of the Drug Interactions subsection, revise, "Warfarin" to read, "warfarin".
- iii. Revise the Carcinogenesis, Mutagenesis, Impairment of Fertility and the Pregnancy subsections as follows:

Carcinogenesis, Mutagenesis, 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 finding 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: Pregnancy 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 daily 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.

d. ADVERSE REACTIONS

- i. Use "extended-release" rather than "controlled-release" throughout this section (including table).
- ii. Make the following revision in the second sentence of the first paragraph, "...200 to 400 mg...", ("to" rather than hyphen).

e. OVERDOSAGE

- i. Let the penultimate sentence, "In addition...", begin a new paragraph.
- ii. Last sentence - ...overdosed...(spelling)

f. DOSAGE AND ADMINISTRATION

- i. Paragraph 1
...extended-release tablet...
- ii. Let the second sentence begin a new paragraph.

g. HOW SUPPLIED

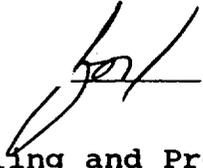
- i. Pentoxifylline Extended-release Tablets are available for....
- ii. Store at controlled room temperature 15°-30°C (59°-86°F)
- iii. Please state that your tablets are unscored.
- iv. Revise your dispensing statement as follows:
"...containers with safety closures."
- v. See comment under CONTAINER above.

Revise your container labels and package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling and final printed container labels. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only.

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

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

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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75028

CORRESPONDENCE

ANDA 75-028

OCT 14 1997

Biovail Corporation International
Attention: Mimi Brennan
460 Comstock Road
Toronto, Ontario
CANADA M1L 4S4

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted December 16, 1996, and found acceptable for filing on February 18, 1997 for Pentoxifylline Extended-Release Tablets, 400 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The report states that "results from rejected batches, if any, are not included in the report".

The rejected runs (if any) and the reason(s) for their rejection are required.

2. The following comment refers to the studies under both fed and fasting conditions:

The Y-scale for the Semi-log Plots are not correct.

3. Additionally, in the Multiple-dose Study, the curve code FKQ41 is missing from the tables summarizing the quality controls values and standard concentrations. Please clarify.
4. The ranges and coefficient of variations (CV%) for all dissolution testing data for each medium should be submitted for both test and reference products at each time point; a dissolution testing method should be suggested; and tentative specifications proposed.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

A handwritten signature consisting of a stylized 'R' followed by a slash and the letter 'S', with a horizontal line extending to the right.

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-028

Biovail Laboratories Inc.
Attention: Arthur Deboeck
#34 Iturregui Avenue
Carolina, Puerto Rico 00983

|||||

FEB 10 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 16, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Pentoxifylline Extended-release Tablets, 400 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

You have failed to provide complete comparative in vitro dissolution data between your proposed product and the reference listed drug. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets.

In addition, the application lacks side-by-side comparisons of the proposed labeling versus the labeling for the reference listed drug with all of the differences annotated and explained. Labeling is defined in the regulations to include both container labels and package insert labeling. Please provide this comparison with all differences annotated and explained as per 314.94 (a)(8)(iv).

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Also, please provide revised certifications for compliance with CGMPs and compliance with federal, state, and local environmental laws from the applicant, Biovail Laboratories Inc., instead of from the parent company.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you

must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3) If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Anna Marie H. Weikel
Project Manager
(301) 594-0315

Sincerely yours,

ISI
Jerry Phillips 2/10/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

B I O V A I L

September 22, 1997

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

Major Amendment

DR label

AC

ATTN: Dr. Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II, Office of Generic Drugs,
Center for Drug Evaluation and Research

**Re: ANDA # 75-028
Pentoxifylline Extended-release Tablets, 400 mg
Reply to FDA Deficiency Letter, dated July 31, 1997 and FDA Fax, dated
August 28, 1997.**

Dear Dr. Holcombe,

Further to your letter dated July 31, 1997 pursuant to Section 505 (j) / 507 of the Federal Food, Drug and Cosmetic Act, Pentoxifylline Extended-release Tablets, 400 mg, we enclose in this major amendment our responses to your questions in the order as they appear in your July 31, 1997 letter.

In the previous ANDA submission, submitted to FDA on December 16, 1997, ANDA # 75-028, Biovail used drug substance from _____ to manufacture Pentoxifylline Extended-release Tablets, 400 mg.

Two additional drug substance manufacturers will be used for the production of commercial batches of Pentoxifylline Extended-release Tablets, 400 mg:

1)

DMF

2)

DMF #



BIOVAIL CORPORATION INTERNATIONAL

B I O V A I L
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The following information is included in this major amendment:

- A signed and dated Form 356h
- Responses to all issues raised in your July 31, 1997 fax of major deficiencies, as well as text revisions as per your additional fax dated August 28, 1997.
- Dissolution profiles of products manufactured with _____ drug substance.
- _____ letters of access to DMFs.
- Pentoxifylline drug substance certificates of analyses from _____
- Pentoxifylline drug substance, granules and tablets quality standard forms (QSFs).
- Commitment to do stability on scale up and commercial batches.

The above information is being sent to you in triplicate (one original and two copies) via Federal Express.

Should you have any questions or comments, please contact me directly at (416) 285-6000 ext. 412 or fax (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL
(On behalf of Biovail Laboratories, Inc.)



George E. Markus, M.Sc.
Manager, Regulatory Affairs

Encl.

077 28 1997



B I O V A I L

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B I O V A I L

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April 9, 1998

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

BIOEQUIVALENCE
Telephone Amendment

ATTN: Dr. Rabindra N. Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Re: **ANDA # 75-028**
Pentoxifylline Extended-release Tablets, 400 mg
Telephone Amendment: Response to Telephone Conversation, dated April 7, 1998

As discussed with Nancy Chamberlin during the April 7, 1998 telephone conversation with Biovail, please find enclosed the requested documentation pertaining to Question 1 of the October 14, 1997 deficiency letter that was issued by the Division of Bioequivalence, OGD regarding Pentoxifylline Extended-release Tablets, 400 mg.

The following information is included in this amendment:

- A signed and dated Form 356h.
- A copy of the rejected run, as requested (Attachment #1), and the reason for rejection.
- A copy of the chromatograms pertaining to the rejected run (Attachment #2).

The above information is being sent to you in triplicate (one original and two copies) via Federal Express.

Should you have any questions or comments, please contact me directly at (416) 285-6000 ext. 212 or fax (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL
(On behalf of Biovail Laboratories, Inc.)



George E. Markus, M.Sc.
Manager, Regulatory Affairs
Encl.

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APR 14 1998

GENERIC DRUGS



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October 29, 1997

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

Amendment

GENERIC AMENDMENT

AB

ATTN: Dr. Rabindra N. Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**Re: ANDA # 75-028
Pentoxifylline Extended-release Tablets, 400 mg
Reply to FDA Deficiency Letter, dated October 14, 1997.**

Please find enclosed our response to the October 14, 1997 deficiency letter that was issued by the Division of Bioequivalence, OGD for Pentoxifylline Extended-release Tablets, 400 mg . All issues have been addressed. For your convenience, we have placed dividers between each of the agency comments / sponsor responses.

The following information is included in this amendment:

- A signed and dated Form 356h.
- Responses to all issues raised in your October 14, 1997 deficiency letter.
- A copy of the October 14, 1997 deficiency letter

The above information is being sent to you in triplicate (one original and two copies) via Federal Express.

Should you have any questions or comments, please contact me directly at (416) 285-6000 ext. 412 or fax (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL
(On behalf of Biovail Laboratories, Inc.)



George E. Markus, M.Sc.
Manager, Regulatory Affairs
Encl.

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OCT 30 1997

GENERIC DRUGS



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N/AC

12 February 1998

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

Major Amendment :
(Requesting Status
Change to
Minor Amendment)

ATTN: Dr. Frank O. Holcombe, Jr., Ph.D., FDA
Director, Division of Chemistry II, Office of Generic Drugs,
Center for Drug Evaluation and Research

Re: **ANDA # 75-028 : Pentoxifylline Extended-release Tablets, 400 mg**
Reply to FDA Deficiency Letter (Fax), dated January 22, 1998

Dear Dr. Holcombe,

Further to your letter dated January 22, 1998 pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act, Pentoxifylline Extended-release Tablets, 400 mg, we enclose in this major (minor – see below) amendment our responses to your questions in the order as they appear in your January 22, 1998 letter. As discussed with Dr. Florence Fang on February 11, 1998 (and previously with Gordon Johnston), a re-assessment of the status of this amendment will take place upon receipt of this response (i.e. "Major" to "Minor").

In the previous ANDA amendment dated September 22, 1997, Biovail had responded to FDA's first deficiency letter and in addition, added two additional drug substance manufacturers for the production of commercial batches of Pentoxifylline Extended-release Tablets, 400 mg :

Biovail has decided to withdraw the additional two active drug substance manufacturers, from the ANDA at this time without prejudice to re-filing. As a result, only drug substance from as listed in our original ANDA submission, will be used to manufacture Pentoxifylline Extended-release Tablets, 400 mg. As all deficiency issues related to the addition of the above two drug substance manufacturers no longer pertain to our ANDA submission, Biovail requests to have the status of this amendment changed from "MAJOR" to "MINOR". The rationale for this change is based on the following:

N.B.
Rw.

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- Deficiency issues 1, 2, 3.c, 5, and 8 no longer apply to this ANDA.

FEB 13 1998

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BIOVAIL CORPORATION INTERNATIONAL

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- Biovail has agreed to all FDA recommendations for the remaining deficiency issues (CMC 3.a, 3.b, 4, 6, 7, and all labelling) and has made every effort to assure that the response to each one is complete and satisfactory.
- With issues 1, 2, 3.c, 5, and 8 no longer applying to this ANDA, the anticipated agency review time for the remaining issues should be less than 1 hour.

Please note that the Pre-Approval Inspection for this application was completed satisfactorily. The Bioequivalence deficiency response has been submitted to the Division on October 29, 1997 and all issues are expected to be resolved satisfactorily. Again, all FDA proposed labelling changes are few and have been incorporated in this amendment. To facilitate the review, all four copies of the revised labelling have been copied onto colour paper and included in this amendment.

We trust that this amendment is complete and satisfactory for filing and review by the Office of Generic Drugs. We look forward to both your acceptance of our request for status change as well as a final approval of this application. Please advise us when your decision has been made regarding Amendment status change.

The above information is being sent to you in triplicate (one original and two copies) via Federal Express.

Should you have any questions or comments, please contact me directly at (416) 285-6000 ext. 212 or fax (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL
(On behalf of Biovail Laboratories, Inc.)



George E. Markus, M.Sc.
Manager, Regulatory Affairs

Encl.

B I O V A I L
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B I O V A I L

OVERNIGHT COURIER

June 15, 1998

AMENDMENT **ORIG AMENDMENT**

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
HFD-610
7500 Standish Place, Room 271N
Rockville, MD 20855

*Labeling
Pentoxifylline
Labeling
6/23/98 G. Vignier*

ATTN: Jerry Phillips
Director, Division of Labelling and Program Support, Office of Generic Drugs,
Center for Drug Evaluation and Research, Food and Drug Administration

**Re: ANDA # 75-028: Pentoxifylline Extended-release Tablets, 400 mg: Finished Product
Labelling**

Dear Mr. Phillips:

Biovail Laboratories Inc is pleased to forward finished printed container labels and insert labelling as requested in your letter of February 12, 1998.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000, extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED



Martin Levy, FBIRA
Manager, Worldwide Regulatory Affairs
Biovail Corporation International

Encl.

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JUN 17 1998
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Anne Marie H. Weikel
3/3/97

February 14, 1997

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

Minor Amendment
Expedited Review Requested
Facsimile Transmittal
Fax To: Anne Marie Weikel
Fax No.: (301)-594-1174

ATTN: Dr. Jerry Phillips
Acting Director, Division of Labeling and Program Support

Re: ANDA # 75-028
Pentoxifylline Extended-release Tablets, 400 mg
Reply to FDA Refusal to File letter, dated February 10, 1997

Dear Dr. Phillips,

Further to your letter dated February 10, 1997 and our acknowledgment amendment dated February 12, 1997, regarding Biovail's Abbreviated New Drug Application dated December 16, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, Pentoxifylline Extended-release Tablets, 400 mg, we enclose in this minor amendment our responses to your questions in the order as they appear in your February 10, 1997 letter.

Question #1

You have failed to provide complete comparative in vitro dissolution data between your proposed product and the reference listed drug. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets.

Response # 1

A complete in-vitro comparative dissolution profiles for Biovail's Pentoxifylline Extended-release Tablets, 400 mg and the reference listed drug, Hoechst-Roussel's Trental[®] Tablets, 400 mg under pH 1.5, 4.5, 6.5, 7.5 and water, are provided for your review in this minor amendment. These dissolution profiles include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets (attachment #1).

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GENERIC DRUGS

BIOVAIL CORPORATION INTERNATIONAL

Question # 2

In addition, the application lacks side-by side comparisons of the proposed labeling versus the labeling for the reference listed drug with all of the differences annotated and explained. Labeling is defined in the regulations to include both container labels and package insert labeling. Please provide this comparison with all differences annotated and explained as per 314.94 (a)8)(iv).

Response #2

Enclosed for your review are, four copies of the side-by-side comparisons of Biovail proposed container labels and insert for Pentoxifylline Extended-release Tablets, 400 mg versus the reference listed drug Trental® Tablets, 400 mg. The differences were annotated and explained as per 314.94 (a)8)(iv) (attachment #2).

Question #3

Please provide revised certifications for compliance with cGMPs and compliance with federal, state, and local environmental laws from the applicant, Biovail Laboratories Inc., instead of from the parent company.

Response #3

A signed and dated Certification for Compliance with cGMPs from Biovail Laboratories Inc., and a signed and dated certification for compliance with federal, state, and local environmental laws from Biovail Laboratories Inc. are enclosed for your review (attachment #3).

On behalf of Biovail Laboratories Inc., we request an expedited review of this minor amendment.

We enclose a signed and dated Form 356h in this minor amendment which is being sent to you in triplicate (one original and two copies) via Federal Express. An exact copy of this minor amendment is faxed to Ms. Anna Marie Weikel's attention in the Office of Generic Drugs.

If you have any questions or comments, please contact Miss Ivy Chung, the contact person at (416) 285-6000 ext. 412, the undersigned at ext. 418 or Arthur Deboeck at (787) 750-5350.

Sincerely,



Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and QA
BIOVAIL CORPORATION INTERNATIONAL

Encl.

B I O V A I L
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NAT
"Will Respond"
Due 2/26/97
NEW CORRESP
NC

February 12, 1997

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

Minor Amendment
Expedited Review Requested

Attention: Jerry Phillips
Director of Labeling and Program Support, Office of Generic Drugs

Dear Mr. Phillips,

Re: ANDA 75-028
PENTOXIFYLLINE EXTENDED-RELEASE TABLETS, 400 MG
Acknowledge Receipt of FDA Letter Dated February 10, 1997

We received today, February 12, 1997, your letter dated February 10, 1997 regarding Biovail Laboratories Incorporated's Abbreviated New Drug Application dated December 16, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Pentoxifylline Extended-release Tablets 400 mg.

As per 21 CFR 314.120, and on behalf of Biovail Laboratories Incorporated, we would like to inform you of our intention to respond to all the deficiencies as listed in the above letter.

A signed and dated FDA 356h Form is enclosed in this amendment which is being sent to you in triplicate (an original and 2 copies).

If you have any questions or comments, please contact Ivy Chung the contact person at (416) 285-6000 ext. 412 or Arthur Deboeck at (787)750-5350 ext. 233.

Sincerely,



Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and QA

Encl.

RECEIVED
FEB 13 1997
GENERIC DRUGS

Arthur Deboeck
2/25/97



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT Biovail Laboratories Inc.	DATE OF SUBMISSION February 12, 1997
ADDRESS (Number, Street, City, State and Zip Code) #34 Iturregui Ave. Carolina, Puerto Rico USA 00983	TELEPHONE NO. (Include Area Code) (416) 285-6000
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued) ANDA 75-028

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN) Pentoxifylline Extended-release Tablets	PROPRIETARY NAME (if any) N/A	
CODE NAME (if any) I08	CHEMICAL NAME Pentoxifylline	
DOSAGE FORM Tablets	ROUTE OF ADMINISTRATION Oral	STRENGTH(S) 400 mg

PROPOSED INDICATIONS FOR USE
Treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

- DMF	- DMF

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
--------------	--------------------------------

TYPE SUBMISSION (Check one)

PRESUBMISSION AN AMENDMENT TO A PENDING APPLICATION SUPPLEMENTAL APPLICATION
 ORIGINAL APPLICATION RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) FEB 13 1997

PROPOSED MARKETING STATUS (Check one)

APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) APPLICATION FOR AN OVER-THE-COUNTER DRUG PRODUCT (OTC)

RECEIVED
FEB 13 1997
GENERIC DRUGS

B I O V A I L
B I O V A I L
B I O V A I L
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*Refer to File
Cecilia H. White
1/27/97*

December 16, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

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DEC 17 1996

GENERIC DRUGS

ATTN: Dr. Douglas Sporn
Office of Generic Drug

**Re: Abbreviated New Drug Application
Pentoxifylline Extended -release Tablets , 400 mg**

Dear Dr. Sporn,

In accordance with the provisions of Section 505(j) of the Federal Food, Drug and Cosmetic Act and Section 314.94 of 21 CFR, and on behalf of the ANDA holder, Biovail Laboratories Incorporated, Biovail Corporation International submits this Abbreviated New Drug Application for Pentoxifylline Extended-release Tablets, 400 mg for three times daily administration. The listed drug used in the bioavailability / bioequivalence studies is the Trental[®] manufactured by Hoechst-Roussel Pharmaceuticals Inc. in USA.

Biovail Laboratories Incorporated, is the ANDA holder of this application. Biovail Corporation International developed, manufactured and tested the product. It is also responsible for compilation of the ANDA for submission. Upon approval, Biovail Laboratories Incorporated will market the product in the USA, under the Biovail Laboratories Incorporated labeling which is submitted in this ANDA.

Biovail Laboratories Incorporated (BLI) is the subsidiary of Biovail Corporation International (BCI). Biovail Laboratories Incorporated has its head office at Chelston Park, Building 2, Collymore Rock, St. Michael, BH1, Barbados, W.I., United States and its manufacturing site at # 34 Iturregui Ave. & B Street, P.O. Box 3468, Carolina, Puerto Rico, 00984, USA.

Biovail Corporation International is located at 2488 Dunwin Drive, Mississauga, Ontario, Canada L5L 1J9. Its manufacturing site is at: 100 LifeSciences Parkway, Box 21390, Steinbach, Manitoba, Canada R0A 2T3.

We trust that this ANDA is complete and satisfactory for review by the Office of Generic Drugs.

1

BIOVAIL CORPORATION INTERNATIONAL

460 COMSTOCK ROAD, TORONTO, ONTARIO, CANADA M1L 4S4 • TEL (416) 752-3636 FAX (416) 752-7610

B I O V A I L

The Archival Copy, the Review Copy, and the Field Copy of this ANDA are being sent to you, today, via Federal Express.

If you have any questions or comments, please contact Ms. Ivy Chung, the main contact person at Biovail Corporation International, telephone number 1-416-752-3636 ext. 240 or the undersigned at 1-416-752-3636 ext. 257.

Sincerely yours,



Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and Quality Assurance
BIOVAIL CORPORATION INTERNATIONAL

Encl.

1A



BIOVAIL CORPORATION INTERNATIONAL

460 COMSTOCK ROAD, TORONTO, ONTARIO, CANADA M1L 4S4 • TEL (416) 752-3636 FAX (416) 752-7610