CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-189

BIOEQUIVALENCE

Nabumetone
750 mg Tablet
500 mg Tablet
ANDA # 75189
Reviewer: Andre J. Jackson
WP# 75189SDW.498

Teva Pharmaceuticals
Sellersville, Pa.
Submission Date:
April 28, 1998

Review of Dissolution Data For The 750 mg and 500 mg Tablets and Waiver Request for 500 mg Tablet

Background

The firm submitted a bioequivalence study on August 18, 1997 on their 750 mg tablet along with a waiver request for the 500 mg tablet. The study was found to be incomplete. Dissolution data submitted by the firm with the medium 2% SLS in buffer was not very discriminating so they were requested to conduct additional dissolution studies with different paddle speeds in 2% SLS in water.

Dissolution

The dissolution study for nabumetone was done as follows: This procedure is not an official USP method.

Apparatus:
Medium:
Volume
No. of Units Analyzed:
Assay:

Comments:

1. The dissolution data for the 500 mg and 750 mg tablets are acceptable. The data at 75 rpm was not reviewed since it was similar to the data presented by the firm at 100 rpm.

Recommendation:

1. The fasting and post-prandial bioequivalence studies conducted by Teva Pharmaceutical on its 750 mg Nabumetone tablet, lot K-22174 comparing it to SmithKline Beecham's Relafen^{R} 750 mg tablet have been found to be acceptable by the Division of Bioequivalence. The 750 mg dosage form of the test product is therefore deemed bioequivalent to the 750 mg tablet of Relafen manufactured by Smithkline Beecham.

2. The dissolution testing conducted by Teva on the 750 mg strength (lot # K22174)and 500 mg strength(lot # K22264)is acceptable. The formulation for the 500 mg tablet is compositionally proportional to the 750 mg tablet which underwent a bioequivalence study. The waiver of in vivo bioequivalence study requirements for the 500 mg tablet is granted. The 500 mg dosage form of the test product is therefore deemed bioequivalent to the 500 mg tablet of Relafen manufactured by Smithkline Beecham.

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

> Not less of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 7/29/98

Concur: Date: 8/6/98
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

Attachment: E-mail with Dissolution Specification

Table 1. In Vitro Dissolution Testing

Drug (Generic Name):Nabumetone
Dose Strength:750 mg
ANDA No.:75-189
Firm:Teva Pharmaceutical
Submission Date:April 28, 1998
File Name:75189DW.498

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 100
No. Units Tested: 12
Medium: 2% SLS in water
Volume:1000mL
Specifications: in 45 min

Reference Drug: Relafen
Assay Methodology:

This is not an official USP method.

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # K-22174 Strength(mg) 750			Reference Product Lot # 70086R52 Strength(mg) 750		
	Mean %	Range	%CV	Mean %	Range	%CV
15	83.2		6.5	90.4		2.3
30	94.2		1.1	98.2		1.2
45	97.8		1.1	99.6		1.2
60	98.5		1.1	99.7		1.3
Sampling Times (Minutes)	Test Product Lot # K-22264 Strength(mg) 500			Reference Product Lot # 50146R51 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	85.5		0.5	90.0		1.6
30	97.2		0.4	97.5		1.4
45	99.6		0.3	98.5		1.5
60	100.3		0.4	98.5		1.4

II. Results of In Vitro Dissolution Testing:-50 RPM						
Sampling Times (Minutes)	Test Product Lot # K-22174 Strength(mg) 750			Reference Product Lot # 70086R52 Strength(mg) 750		
	Mean %	Range	%CV	Mean %	Range	%CV
15	72.2		2.9	50.5		17.2
30	86.4		3.3	84.0		8.4
45	92.0		2.5	95.2		2.6
60	94.4	[illegible]	4.1	98.2		1.7
Sampling Times (Minutes)	Test Product Lot # K-22264 Strength(mg) 500			Reference Product Lot # 50146R51 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	61.7		6.6	70.4		17.8
30	83.6		4.5	87.1		10.0
45	88.0		2.1	95.5		5.3
60	89.6		1.4	98.3		1.9

Nabumetone
750 mg Tablet
500 mg Tablet
ANDA # 75189
Reviewer: Andre J. Jackson
WP# 75189SDW.897

Teva Pharmaceuticals
Sellersville, Pa.
August 18, 1997
December 17, 1997

Review of Bioequivalence Study for 750 mg Tablet, Dissolution Data and Waiver Request for 500 mg Tablet

OBJECTIVE

The objective of this study was to compare the bioavailability of TEVA Pharmaceuticals USA and SmithKline Beecham Pharmaceuticals (Relafen®) 750 mg nabumetone tablets under fasting conditions.

BACKGROUND AND PHARMACOKINETICS

Nabumetone is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. It inhibits prostaglandin synthesis, but its action is otherwise unknown. It is indicated for acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis. The recommended initial dose is 1000 mg daily. Doses exceeding 2000 mg per day have not been studied.

Nabumetone is completely absorbed after oral administration. The parent compound is a prodrug which has little or no pharmacologic activity, but undergoes extensive first pass metabolism to the active component, 6-methoxy-2-naphthylacetic acid (6-MNA). Appreciable concentrations of the parent drug have not been detected in the plasma.

The administration of food increases the rate of absorption and subsequent appearance of 6-MNA in the plasma but does not effect the extent of conversion of nabumetone into 6-MNA. Peak plasma concentrations of 6-MNA are increased by approximately one-third.

Mean tmax values ranging from 2 to 13 hours have been observed. Possible explanations for the variation include individual differences in absorption of the parent compound and differences in metabolism.

Approximately 35% of a 1000 mg nabumetone dose is converted to 6-MNA and 50% is converted into unidentified metabolites. At therapeutic doses, 6-MNA is more than 99% bound to plasma protein. Elimination of the drug is mainly renal with approximately 75% of a dose recovered in the urine within 48 hours. Over the 7 days following an oral dose, approximately 80% of the dose is excreted in the urine, and a further 9% in the feces.

Methods

The study was conducted by Phoenix International Montreal Quebec Canada under the clinical direction of Pierre Geoffroy,

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STUDY DESIGN

Open-label, randomized, 2-way crossover, comparative bioavailability study under fasting conditions.

No. of Subjects 32 healthy non-smoking adult male subjects were enrolled; dropouts were not replaced.

SUBJECT SELECTION

Subjects

This study involved non-smoking male subjects, 18-45 years of age, weighing at least 60 kg, who were within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983).

Screening

Subjects were screened within 14 days of Period 1 dosing. Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking history was recorded. Each subject received a complete physical examination and the laboratory tests of hematologic, hepatic and renal functions listed below. Only

medically healthy non-smoking subjects with clinically normal laboratory profiles were enrolled in the study.

Subjects received the following laboratory tests:

1. Hematology

   Hemoglobin
   Hematocrit
   Total and differential
   Leukocyte count
   Red blood cell count
   Platelet count

2. Serum Chemistry (fasting)

   BUN
   Creatinine
   Total bilirubin
   Alkaline phosphatase
   SGOT
   SGPT
   Sodium
   Potassium
   Glucose

3. Urinalysis

   pH
   Specific gravity
   Protein
   Glucose
   Ketones
   Bilirubin
   Blood
   Nitrite
   Urobilinogen
   Microscopic examination

4. HIV test

5. Hepatitis B

6. Urine drug screen. (alcohol, cocaine and cannabinoids)

Exclusions

History or presence of significant:

cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, necrologic or psychiatric disease.

More specifically, history or presence of significant:

peptic ulcer disease.

In addition, history or presence of:

alcoholism or drug abuse within the past year.
hypersensitivity or idiosyncratic reaction to nabumetone, naproxen or other nonsteroidal antiinflammatory drugs.

Subjects with any medical condition requiring regular treatment with prescription drugs.

The use of any pharmacological agents known to significantly induce or inhibit drug-metabolizing enzymes within 30 days of study start.

Subjects who had been on an abnormal diet (for whatever reason) during the four weeks preceding the study.

Subjects who, through completion of this study, would have donated more than 500 mL of blood and/or plasma in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 mL in a year.

No subject may smoke (both cigarettes and tobacco related products) for 90 days preceding the study and throughout the course of the study.

Subjects who have participated in another clinical trial within 30 days of study start.

Subjects who do not tolerate venipuncture.

Prohibitions

No subjects were allowed to take prescription medication within 14 days prior to dosing and during the course of the study, or take over-the-counter medication (including vitamins) within 7 days prior to dosing and throughout the course of the study.

The consumption of alcohol- or xanthine-containing beverages and foods were prohibited for 48 hours before dosing and throughout the periods of sample collection.

If drug therapy other than that specified in the protocol is required during the time of sample collection, or during the washout period between drug administrations, a decision to continue or discontinue the subject was made by the Study Physician (or medically-qualified designate) or Principal Investigator, based on the time the medication was administered and its pharmacology and pharmacokinetics.

CLINICAL PROCEDURES

Drug Administration

After a supervised overnight fast of at least 10 hours, subjects received an oral dose of the assigned formulation, with 240 mL of water according to the following randomization scheme.

Sequence AB	1,2,5,7,9,11,15,16,17,18,21,24,27,28,29
Sequence BA	3,4,6,8,10,12,13,14,19,20,22,23,25,26,30, 31,32

A-Test B-Reference

The products employed in the study were:
1.Reference product Relafen®, SmithKline Beecham
Lot # 7008 6R52 Expiration Date-August 31, 1998, potency 98.8%.

2.Test product-Nabumetone, Teva Pharmaceutical
Lot # K-22174, Manufacturing Date-February 12, 1997,
potency 97.9%, lot size

There was a 14 day washout period between doses.

The formulation for the 750 mg Tablet was:

Ingredient	Mg/Tablet

Blood Sampling

Blood samples were collected before dosing and at the following times thereafter: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48, 72, 96 and 120 hours. Samples were cooled in an ice bath and centrifuged under refrigeration as soon as possible. Plasma samples were divided into 2 portions and stored in suitably labeled tubes at -12°C or lower, pending assay. The location of venipuncture was varied from one draw to the next in order to minimize subject discomfort.

Activity

Subjects avoided vigorous exertion and complete rest for the first 4 hours after drug administration.

Adverse Reactions

Subjects were monitored throughout confinement for adverse reactions to the study formulations and/or procedures. The Study Physician, or a monitoring physician, was on site for drug administration and for 4 hours thereafter, and on call for the remainder of the study. At the time of the 36-hour, and subsequent, blood collections in each study

period, each subject was asked how he was feeling. Treatment of any adverse reactions was administered by a physician, either at Phoenix or at a nearby hospital emergency room. The Sponsor was notified of any serious adverse reactions within 1 working day and of all other adverse reactions within 5 working days.

At the beginning of the second period, subjects were questioned concerning unusual symptoms which may have occurred after the previous administration of the study drugs. Drug-related symptoms of clinical significance were evaluated by the Study Physician or a monitoring physician before the next dose was administered.

All adverse reactions and treatment administered were recorded in the final report.

ETHICAL CONSIDERATIONS

Basic Principles

This research was carried out in accordance with the clinical research guidelines established by the Medical Research Council of Canada, the Basic Principles defined in the U.S. 21 CFR Part 312.20 and the principles enunciated in the Declaration of Helsinki (Hong Kong, 1989).

Institutional Review Board

This protocol was reviewed by the Phoenix International Life Sciences Institutional Review Board and the study did not start until the Board had approved the protocol or a modification thereof. The Board was constituted and operates in accordance with the principles and requirements described in "Guidelines on Research Involving Human Subjects" (Medical Research Council of Canada, 1987) and in the U.S. Code of Federal Regulations (21 CFR Part 56).

Informed Consent

The purpose of the study, the procedures to be carried out

and the potential hazards was described to the subjects in non-technical terms. Subjects were required to read, sign and date a consent form summarizing the discussion prior to enrollment, and were assured that they could withdraw from the study at any time without jeopardizing their medical care.

Subjects were given a copy of their consent forms.

Indications for Subject Withdrawal

Subjects were free to withdraw at any time for any reason, or they were withdrawn if necessary to protect their health or the integrity of the study. The final report included reasons for withdrawals.

DATA ANALYSIS

Pharmacokinetic Analysis

Pharmacokinetic parameters for plasma 6-methoxy-2-naphthylacetic acid were calculated as follows:

AUC 0-t: The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, was calculated by the linear trapezoidal method.

AUCinf: The area under the plasma concentration versus time curve from time 0 to infinity. AUCinf was calculated as the sum of the AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.

AUC/AUCinf: The ratio of AUC 0-t to AUCinf.

Cmax: Maximum measured plasma concentration over the time span specified

tmax: Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, tmax was defined as the first time point with this value.

kel: Apparent first-order elimination or terminal

rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis using the last three (or more) non-zero plasma concentrations.

t 1/2: The elimination or terminal half-life was calculated as 0.693/kel.

No value of kel, AUCinf or t ½ was reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Statistical Analyses

Statistical analyses, including the following, were performed for plasma 6-methoxy-2-naphthylacetic acid data. Data from only those subjects who completed the crossover were submitted for statistical analyses, with unbalanced groups being used if necessary.

Analytical Method

Sample analysis was conducted between June 25, 1997 and July 11, 1997. Therefore, the total time for sample storage was approximately 2 weeks.

Assay sensitivity:

The assay was linear over the range of 0.1 to 50 ug/mL. The limit of sensitivity of the assay was defined as 0.1 ug/mL, with values less than this

reported as zero.

Precision and Reproducibility:

Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 7.6% at a concentration of 0.1 ug/mL and 4.7% at 50 ug/mL.

Accuracy

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. Accuracy was 102.3% at 0.3 ug/mL and 100.2% at 39.89 ug/mL. Respective coefficients of variation at these concentrations were 4.2% and 3.6% respectively.

Pre-assay Validation

Long Term (Frozen) data shows the compound to be stable for 13 days at a nominal temperature of -22°C. Extended Long Term stability, at a nominal temperature of -22°C, proved 6-Methoxy Naphthalene Acetic Acid to be stable for a period of at least 216 days. The Long Term Stability evaluation involved the analysis of replicates of stored samples at approximate concentrations of the low and the high QCs (Stability Samples) which have been kept under typical temperature and light conditions for the designated time of storage, with freshly spiked samples from a similar number of replicates at the approximate concentrations of the low and high QCs(Comparison Samples). This evaluation used chromatographic responses; i.e. peak height ratio to internal standard.

The short term stability evaluation involved an analysis of replicates of stability samples which had been kept under typical temperature and light conditions for a designated time, with freshly thawed comparison samples, each at approximately the concentration of the high and low QCs.

The freeze-thaw stability evaluation involved an analysis of replicates of stability samples which had been frozen and thawed five times, with freshly thawed (once only) comparison samples, each at approximately the concentration of the high and low QCs.

The Stock solution Stability evaluation involved an analysis of 10 replicates of stock stability samples which had been kept at a nominal temperature of -22°C with 10 freshly prepared stock comparison samples.

The autosampler stability was evaluated while running a method evaluation batch. The results were obtained by using the standard curve to calculate the values for QC samples, then comparing the percentage of deviation (I Dev) of each individual QC sample from the mean.

The extended autosampler stability evaluated QC samples which were injected at the beginning of the run and at the maximum time for which autosampler stability had been previously documented (21.3 hours) and approximately every 12 hours thereafter.

The Wet Extract Stability evaluation involved an analysis of replicates, which were extracted and stored for a designated time at the nominal temperature of 4°C (Stability Samples), with freshly extracted Comparison Samples, each at approximately the concentrations of the low and high QCs.

The spiking solution stability evaluation involved an analysis of replicates of spiking solution (stability) samples at approximately the concentrations of low and high QCs, which have been kept at a nominal temperature of -22°C , with freshly prepared spiking solution (comparison) samples also at approximately the concentrations of low and high QCs.

The recoveries were calculated by comparing a calibration curve prepared in extracted blanks representing 100% recovery with extracted QCs. The results are given in Appended Table 1 for 6-Methoxy Naphthalene Acetic Acid and in Appended Table

2 for the Internal Standard at the concentrations of 101.32 mcg/mL and 202.64 mcg/mL.

Dilution Integrity: The Dilution Integrity of 6-Methoxy Naphthalene Acetic Acid was determined by preparing a QC sample with a concentration equivalent to four times the highest standard, followed by dilutions of 1:5 and 1:10 in human plasma. Refer to Appended Table 3 for the results of the Dilution Integrity test.

Stability Data: Long Term, Extended Long Term, Short Term (benchtop), Freeze-Thaw, Stock Solution, Wet Extract and Spiking Solution Stabilities are provided in Appended Tables 4-13 respectively.

RESULTS

Subject Drop-outs

32 subjects were enrolled in the study. Subject numbers 1, 20, and 29 withdrew. Subject #1 withdrew for personal reasons after the 36 hr blood draw. Subject #20 withdrew prior to period 2 and #29 withdrew 5 days after period 1 dosing. Therefore, 29 subjects completed the study.

Table 1. 6-methoxy-2-naphthylacetic acid mean plasma levels, ug/mL (±sd), for the subjects that received the test and reference formulations after an overnight fast(N=29).

Sample Time	Test	Reference
0.0	0.00(0.00)	0.00(0.00)
0.5	3.3(2.6)	4.65(3.03)
1.0	7.9(4.9)	13.01(5.71)
1.5	10.82(6.14)	16.99(5.32)
2.0	13.09(6.72)	19.06(5.53)
3.0	16.55(7.08)	20.97(5.89)

4.0	18.41(7.61)	22.16(6.14)
5.0	19.08(6.36)	22.35(6.24)
6.0	19.14(6.13)	21.93(5.50)
7.0	18.61(5.42)	22.00(5.57)
8.0	18.84(5.65)	21.47(5.20)
9.0	18.70(5.79)	21.16(5.13)
10.0	17.79(5.13)	21.63(6.31)
11.0	17.52(4.85)	20.43(4.58)
12.0	17.25(4.68)	20.01(4.87)
13.0	17.41(4.69)	20.03(4.33)
14.0	16.67(4.55)	19.60(4.64)
16.0	17.19(4.39)	19.38(4.23)
24.0	16.82(3.44)	19.00(3.98)
36.0	13.69(3.55)	14.83(3.45)
48.0	10.31(3.31)	10.66(2.76)
72.0	5.14(2.08)	5.19(1.86)
96.0	2.50(1.35)	2.51(1.67)
120.0	1.26(0.85)	1.29(0.75)

Table2.Summary of Mean Bioavailability Parameters for 6-methoxy-2-naphthylacetic acid. Parameters are for arithmetic and geometric means. Values are mean ± %cv. (N=29)

	Test		Reference		
Variable	Mean	%CV	Mean	%CV	Ratio T/R
AUCL[1] ug/mL x hr	1049.4	24.8	1146.4	22.9	0.915

LAUCL	1017.21[3]	26.4	1112.09	27.1	0.915
AUCI[2] ug/mL x hr	1095.4	26.7	1192.9	24.3	0.918
LAUCI	1057.11	28.2	1153.47	28.5	0.916
CMAX ug/mL	22.01	29.9	24.66	26.5	0.892
LCmax	21.13	29.6	23.77	28.9	0.888
TMAX hr	10.38	84.8	8.82	79.6	----
KELM hr-1	0.031	16.7	0.031	15.4	----
THALF hr	22.86	18.6	23.02	23.03	----

1.AUC to the last measurable plasma concentration
2.AUC to infinity
3.Geometric mean

Table 3.90% Confidence Intervals
Parameter

LnAUCL	87.0-96.3
LnAUCI	87.0-96.6
LCmax	82.1-96.8

Adverse Effects

Adverse effects are given in vol 1.2 pages 206-209. Most effects were minor and were primarily seen with the test product.

Sample Repeats

There were no sample repeats reported by the firm for the 1390 samples analyzed Appended Table 14.

Review of Post-Prandial Bioequivalence Study for the 750 Mg Nabumetone Tablet

Objective

The objective of this study was to compare the bioavailability of TEVA Pharmaceuticals and SmithKline Beecham Pharmaceuticals 750 mg nabumetone tablets under fed conditions.

Methods

The study was conducted by Phoenix International Montreal Quebec Canada under the clinical direction of Pierre Geoffroy, M.D. Samples were analyzed at Phoenix under the direction of Pharm.D. Period I dosing was done on May 24, 1997, period II on June 7, 1997 and period III on June 21, 1997.

STUDY DESIGN

Open-label, randomized, 3-way crossover, comparative bioavailability study under fed and fasting conditions.

No. of Subjects 18 healthy non-smoking adult male subjects were enrolled; dropouts were not replaced.

SUBJECT SELECTION

Subjects

This study involved non-smoking male subjects, 18-45 years of age, weighing at least 60 kg, who were within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983).

Screening

Subjects were screened within 14 days of Period 1 dosing. Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking history will be recorded. Each subject received a complete physical examination and the laboratory tests of hematologic, hepatic and renal functions listed below. Only medically healthy non-smoking subjects with clinically normal laboratory profiles were enrolled in the study.

Inclusion and exclusion criteria as well as study prohibitions were the same as for the fasting study.

CLINICAL PROCEDURES

Drug Administration

Regimen A: After a supervised overnight fast of at least 10.5 hours, subjects received an oral dose of the assigned formulation, with 240 mL of water, according to a randomization scheme to be generated at Phoenix International Life Sciences.

Regimens B & C: After a supervised overnight fast of at least 10 hours and 30 minutes before their scheduled dosing times, subjects received a standard breakfast consisting of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 rasher of Canadian bacon, 120 g hash brown potatoes, 180 mL of orange juice and 240 mL whole milk. At the scheduled dosing times, each subject was given an oral dose of the assigned formulation, with 240 mL of water, according to the following randomization scheme generated at Phoenix International Life Sciences.

RANDOMIZATION SCHEME

A= TEVA Pharmaceuticals USA 1 x 750 mg nabumetone tablet (fasting)
B= TEVA Pharmaceuticals USA 1 x 750 mg nabumetone tablet

(fed)
C= SmithKline Beecham (Relafen®) 1 x 750 mg nabumetone tablet (fed)

Subject ID	Study Period		
	1	2	3
1	C	B	A
2	A	B	C
3	A	B	C
4	A	C	B
5	A	C	B
6	B	A	C
7	C	B	A
8	B	C	A
9	B	C	A
10	B	A	C
11	A	C	B
12	C	A	B
13	A	B	C
14	C	A	B
15	C	A	B
16	B	C	A
17	C	B	A
18	B	A	C

The products employed in the study were:
1.Reference product Relafen®, SmithKline Beecham
Lot # 7008 6R52 Expiration Date-August 31, 1998, potency 98.8%.

2.Test product-Nabumetone, Teva Pharmaceutical
Lot # K-22174, Manufacturing Date-February 12, 1997, potency 97.9%, lot size

There was a 14 day washout period between doses.

Blood Sampling

Blood samples were collected before dosing and at the following times thereafter: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48, 72, 96 and 120 hours. Samples were cooled in an ice bath and centrifuged under refrigeration as soon as possible. Plasma samples were divided into 2 portions and stored in suitably labeled tubes at -12°C or lower, pending assay. The location of venipuncture was varied from one draw to the next in order to minimize subject discomfort.

Activity

Subjects avoided vigorous exertion and complete rest for the first 4 hours after drug administration.

Adverse Reactions

Subjects were monitored throughout confinement for adverse reactions to the study formulations and/or procedures. The Study Physician, or a monitoring physician, was on site for drug administration and for 4 hours thereafter, and on call for the remainder of the study. At the time of the 36-hour, and subsequent, blood collections in each study period, each subject was asked how he was feeling. Treatment of any adverse reactions was administered by a physician, either at Phoenix or at a nearby hospital emergency room. The Sponsor was notified of any serious adverse reactions within 1 working day and of all other adverse reactions within 5 working days.

At the beginning of the second and third periods, subjects were questioned concerning unusual symptoms which may have occurred after the previous administration of the study drugs. Drug-related symptoms of clinical significance were evaluated by the Study Physician or a monitoring physician before the next dose was administered.

All adverse reactions and treatment administered were recorded in the final report.

ETHICAL CONSIDERATIONS

Basic Principles

This research was carried out in accordance with the clinical research guidelines established by the Medical Research Council of Canada, the Basic Principles defined in the U.S. 21 CFR Part 312.20 and the principles enunciated in the Declaration of Helsinki (Hong Kong, 1989).

Institutional Review Board

The protocol was reviewed by the Phoenix International Life Sciences Institutional Review Board and the study did not start until the Board had approved the protocol or a modification thereof. The Board was constituted and operated in accordance with the principles and requirements described in "Guidelines on Research Involving Human Subjects" (Medical Research Council of Canada. 1987) and in the U.S. Code of Federal Regulations (21 CFR Part 56).

Informed Consent

The purpose of the study, the procedures to be carried out and the potential hazards were described to the subjects in non-technical terms. Subjects were required to read, sign and date a consent form summarizing the discussion prior to enrollment, and be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects were given a copy of their consent forms.

Indications for Subject Withdrawal

Subjects were free to withdraw at any time for any reason,

or they may be withdrawn if necessary to protect their health or the integrity of the study. The final report included reasons for withdrawals.

Termination of the Study

Phoenix and the Sponsor each reserved the right to terminate the study in the interest of subject welfare.

DATA ANALYSIS

Pharmacokinetic Analysis

Pharmacokinetic parameters for plasma 6-methoxy-2-naphthylacetic acid were calculated as follows:

AUC 0-t: The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

AUCinf: The area under the plasma concentration versus time curve from time 0 to infinity. AUCinf was calculated as the sum of the AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.

AUC/AUCinf: The ratio of AUC 0-t to AUCinf.

Cmax: Maximum measured plasma concentration over the time span specified.

tmax: Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, tmax was defined as the first time point with this value.

kel: Apparent first-order elimination or terminal rate constant calculated from a semi-log plot

of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis using the last three (or more) non-zero plasma concentrations.

t1/2: The elimination or terminal half-life was calculated as 0.693/kel.

No value of kel, AUCinf or t1/2 was reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Statistical Analyses

Statistical analyses, including the following, were performed for plasma 6-methoxy-2-naphthylacetic acid data. Data from only those subjects completing at least Regimens B and C of the study were submitted for statistical analyses, with unbalanced groups being used if necessary.

DATA ANALYSIS

Analyses of variance was performed on the untransformed pharmacokinetic parameters listed above, with the exception of the ratio AUC 0-t to AUCinf. Additionally, log-transformed data was used for analysis of AUCinf, AUC 0-t and Cmax. The analysis of variance model included subjects, period, first-order carryover and drug formulation as factors. A 5% level of significance was used. Each analysis of variance included calculation of least-squares means, adjusted differences between formulation means and the standard error associated with these differences. The above statistical analyses was done using the SAS GLM procedure.

Ratio Analyses

Ratios of means was calculated using the LSM for both untransformed and log-transformed AUC 0-t, AUCinf and Cmax. The geometric mean values was reported for log-transformed parameters. Ratios of means were expressed as a percentage.

The comparisons of interest are: B vs A and B vs C.

ANALYTICAL PROCEDURES

Samples from subjects completing at least Regimens B and C of the study were assayed for 6-methoxy-2-naphthylacetic acid using chromatographic procedures developed at Phoenix International Life Sciences. Whenever possible, all samples from each subject were analyzed on the same standard curve. Standard and quality control samples were distributed through each batch of study samples assayed. Samples with drug concentrations greater than the upper limit of the validated range of the assay were diluted with the appropriate drug-free biological fluid and reassayed; those which were below the lower limit of this range will be reported as being below LOQ. Repeat assays, when necessary, were performed on the second tube of frozen sample rather than on the remainder from the first tube, wherever possible. The analysts did not have access to the randomization scheme. Samples from dropouts were not assayed unless the subject completed at least regimens B and C of the study.

Analytical Method

Sample analysis was conducted between June 30, 1997 and July 15, 1997. Therefore, the total time for sample storage was approximately 2 weeks.

Assay sensitivity:

The assay was linear over the range of 0.1 to 50.28 ug/mL. The limit of sensitivity of the assay was defined as 0.1 ug/mL, with values less than this reported as zero.

Precision and Reproducibility:

Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 5.1% at a concentration of 0.1 ug/mL and 3.2% at 50.28 ug/mL.

Accuracy

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. Accuracy was 100.5% at 0.3 ug/mL and 99.4% at 39.89 ug/mL. Respective coefficients of variation at these concentrations were 4.4% and 2.6% respectively.

Pre-assay validation was the same as for the fasting study.

RESULTS

Table 3. 6-methoxy-2-naphthylacetic acid mean plasma levels, ug/mL (±sd), for the subjects that received the test following an overnight fast and the test and reference formulations with food. (N=18)

Sample Time	Test-Fasting	Test-Fed	Reference-Fed
0.0	0.00(0.00)	0.00(0.00)	0.00(0.00)
0.5	3.8(2.4)	2.57(4.03)	2.51(2.57)
1.0	9.8(3.3)	9.41(7.72)	14.97(10.93)
1.5	12.65(4.18)	17.48(9.53)	23.99(13.37)
2.0	14.32(4.85)	23.65(9.29)	28.64(11.21)
3.0	16.72(5.27)	28.41(8.70)	33.95(9.40)
4.0	17.89(5.63)	32.40(7.94)	34.35(7.81)
5.0	18.10(6.39)	33.11(7.54)	33.35(8.02)
6.0	18.12(6.43)	30.40(7.41)	31.22(7.75)
7.0	17.60(5.86)	29.31(6.70)	29.42(7.24)
8.0	16.85(5.70)	27.33(6.23)	27.22(7.19)
9.0	16.76(5.63)	27.12(6.05)	26.86(6.74)
10.0	16.31(5.30)	25.25(5.56)	26.08(6.40)
11.0	15.99(5.43)	25.01(5.66)	25.21(6.28)
12.0	15.99(5.30)	24.31(5.59)	24.62(6.11)
13.0	15.47(4.88)	24.06(5.45)	22.42(6.16)
14.0	15.50(5.12)	22.35(5.19)	22.71(5.44)
16.0	15.23(4.59)	21.45(5.25)	21.45(5.15)
24.0	16.51(4.72)	18.08(4.23)	18.20(4.78)

36.0	13.72(3.82)	13.00(3.42)	13.00(3.26)
48.0	10.41(3.01)	8.84(2.52)	8.80(2.61)
72.0	5.33(1.83)	4.38(1.71)	4.44(1.57)
96.0	2.66(1.01)	2.30(0.86)	2.26(0.93)
120.0	1.38(0.60)	1.36(0.77)	1.16(0.57)

Table 4. Summary of Mean Bioavailability Parameters for 6-methoxy-2-naphthylacetic acid. Parameters are arithmetic and geometric means for the test and reference formulations following a high fat meal or the test under fasting conditions. Values are mean (± %cv). (N=18)

Variable	Test-Fasting	Test-Fed	Reference-Fed	Ratio-Fed T/R
LAUCL[1] ug/mLxhr	998.66[3] (28.4)	1120.45 (25.7)	1131.40 (28.5)	0.99
LAUCI[2] ug/mLxhr	1046.51 (28.6)	1158.67 (27.1)	1170.76 (29.1)	0.99
LCMAX ug/mL	18.56 (34.4)	33.93 (22.1)	35.76 (27.3)	0.95
KEL hr-1	0.029 (12.6)	0.028 (13.7)	0.029 (13.3)	
HALF-LIFE hr	24.39 (12.6)	24.87 (14.4)	24.26 (14.4)	
TMAX hr	10.41 (92.6)	4.39 (24.9)	3.47 (32.9)	

1.AUC to the last measurable plasma concentration
2.AUC to infinity
3.Geometric mean

Adverse Effects

Adverse effects are listed in volume 1.6 pages 1449-1459. Most effects were minor and were primarily seen with the test product.

Sample Repeats

There were 3 sample repeats reported by the firm out of 1296 samples analyzed. This data is presented in Appended Table 15.

Subject Drop-outs

There were no subject drop-outs.

Dissolution

The dissolution study for nabumetone was done as follows: This procedure is not an official USP method.

Apparatus:	Paddle, 100 RPM
Medium:	2% SLS in 0.1M
	1000mL Phosphate Buffer pH 7.4
No. of Units Analyzed:	12
Specifications:	NLT in 45 minutes
Assay:	

Waiver of In Vivo Requirement for 500 mg Tablet

The comparative formulations for the 750 mg and 500 mg tablets are presented in Appended Table 16 and the dissolution is in Table 17.

Comments:

1. The 90% confidence intervals for the test product for the parameters LCmax, LnAUC(0-t) and LNAUC(0-inf) are within the acceptable limits of 80-125% of the reference product for the fasting study.

2. The non-fasting study is acceptable.

3. The 500 mg tablet is compositionally proportional to the 750 mg tablet that underwent bioequivalency testing.

4. The dissolution data for the 500 mg and 750 mg tablets are incomplete.

Deficiency:

1. The firm should submit dissolution data using 2% SLS in water as the dissolution medium. The dissolution for the product should be investigated at paddle speeds of 75 and 50 rpms using this medium.

Recommendation

1. The fasting and post-prandial bioequivalence studies conducted by Teva Pharmaceutical on its 750 mg Nabumetone tablet, lot K-22174 comparing it to SmithKline Beecham's Relafen[R] 750 mg tablet have been found to be incomplete by the Division of Bioequivalence.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 2/4/98

Concur: Date: 2/4/98
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

Table 17. In Vitro Dissolution Testing

Drug (Generic Name):Nabumetone
Dose Strength:750 mg
ANDA No.:75-189
Firm:Teva Pharmaceutical
Submission Date:August 18, 1997
File Name:75189SDW.897

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 100
No. Units Tested: 12
Medium: 2% SLS in pH 7.4 phosphate buffer
Volume:1000mL
Specifications: NLT in 45 min

Reference Drug: Relafen
Assay Methodology:

This is not an official USP method.

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # K-22174 Strength(mg) 750			Reference Product Lot # 70086R52 Strength(mg) 750		
	Mean %	Range	%CV	Mean %	Range	%CV
15	79.9		3.8	77.3		8.9
30	93.2		1.3	96.2		1.8
45	98.1		0.7	100.6		1.6
60	99.9		0.7	101.6		1.9
Sampling Times (Minutes)	Test Product Lot # K-22264 Strength(mg) 500			Reference Product Lot # 50146R51 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	84.9		1.2	88.6		1.2
30	96.5		1.9	96.8		4.1
45	99.6		1.9	98.6		2.8
60	100.5		1.5	99.1		2.8

TABLE T4.2 PROJECT NO.72012/EPX

Absolute Recovery of 6-Methoxy Naphthalene Acetic Acid in Human Plasma

CURVE CODE	QC A (0.30 mcg/mL)		QC B (20.00 mcg/mL)		QC C (40.01 mcg/mL)	
	CALCULATED CONCENTRATION		CALCULATED CONCENTRATION		CALCULATED CONCENTRATION	
	QC A mcg/mL	% RECOVERY	QC B mcg/mL	% RECOVERY	QC C mcg/mL	% RECOVERY
EPX 15	0.31	101.7	20.13	100.7	43.90	109.7
	0.31	103.7	21.01	105.1	44.09	110.2
	0.33	109.7	21.34	106.7	43.65	109.1
	0.32	108.1	20.84	104.2	44.53	111.3
	0.32	107.4	21.81	109.0	44.41	111.0
	0.31	103.4	21.35	106.7	45.24	113.1
	0.34	113.2	20.47	102.4	43.74	109.3
	0.33	110.5	21.54	107.7	42.11	105.2
	0.35	115.2	21.81	109.1	43.11	107.7
	0.34	113.1	21.29	106.4	42.84	107.1
MEAN	0.326	108.60	21.159	105.80	43.762	109.37
SD	0.0143	4.596	0.5514	2.735	0.9030	0.273
% CV	4.4	4.2	2.6	2.6	2.1	2.1
N	10	10	10	10	10	10