CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-920

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-920
Submission Dates	4/18/2005; 7/28/2005
Brand Name	N/A (OTC product)
Generic Name	Naproxen Sodium
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	DCPB2
OND Division	Office of Non-Prescription Products/Division of Non-Prescription Clinical Evaluation
Applicant	Banner Pharmacaps, Inc.
Relevant IND	IND 71,161
Type of Submission; Code	505 (b)(2); 3S
Formulation; Strength(s)	Liquid-filled Soft Gelatin Capsules, 220 mg
Indication	OTC use for- Temporarily relieves minor aches and pains due to: headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, menstrual cramps, and temporarily reduces fever

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1 EXECUTIVE SUMMARY

Naproxen sodium belongs to the nonsteroidal anti-inflammatory class of drugs (NSAIDs). It inhibits the synthesis of prostaglandins in body tissues by inhibiting cyclooxygenases (COX). Naproxen inhibits both COX-1 and COX-2. Naproxen sodium was approved in 1976 for prescription use (275 mg and 550 mg). The prescription indications include - treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, tendonitis, bursitis, acute gout, and the management of pain and primary dysmenorrheal. In 1994, FDA granted over-the-counter (OTC) approval for naproxen sodium 220 mg for the indication of the temporary relief of minor aches and pains due to headache, muscular aches, minor pain or arthritis, toothache, backache, common cold, and menstrual cramps; the temporary reduction of fever. The maximum daily OTC dose is 660 mg. Consumers should not exceed two tablets (440 mg) in any twelve hour period.

In this 505 (b)(2) NDA application, the sponsor is seeking approval for naproxen sodium liquid-filled soft gelatin capsules, 220 mg, a new dosage form for the OTC indication. The listed reference compound is ALEVE® tablets, 220 mg, manufactured by Bayer Healthcare (NDA 20-204).

The applicant is relying on the Agency's findings of the safety and efficacy of the approved ALEVE product (including preclinical, toxicology and clinical data) to support the safety and clinical portion of this application.

The Labeling, Chemistry and Manufacturing Controls (CMC), and Human Pharmacokinetics and Bioavailability Sections of this application are based on the new formulation. In terms of clinical pharmacology and biopharmaceutics aspects, this application is supported by two pharmacokinetic studies (PRACS R03-725 and PRACS R03-739) and a comparative dissolution study — J4-264A). Studies PRACS R03-725 and PRACS R03-739 assessed for the proposed product relative to ALEVE, the relative bioavailability under fasting conditions and effect of a high fat meal.

Naproxen sodium liquid-filled soft gelatin capsules 220 mg (test) was bioequivalent to ALEVE tablets 220 mg (reference) under fasting conditions based on C_{max} and AUC. A delay in T_{max} was observed with the liquid-filled soft gelatin capsules (T_{max} was approximately 25 min later compared to ALEVE). However, this delay may not be clinically detectable because the effective concentration was reached by about 30 min for both the test and the reference products.

Food decreases the rate of absorption of naproxen but not the extent of absorption for both the test and reference compounds. For the test compound, naproxen sodium 220 mg soft gelatin capsules, C_{max} was 20% lower and T_{max} was 2.3 hr longer under fed conditions. This delay may

not be clinically desirable because the effective concentration would not be reached until about 1.5 to 2 hours based on mean plasma-concentrations time profile. NSAIDs are generally taken with food to minimize potential GI side effects. However, in this case, taking the product with food may delay the onset of analgesic effect. This finding would be brought to the attention of the Clinical Reviewer for labeling considerations.

The ALEVE tablet was approved for patients 12 years and above. The Sponsor requested a pediatric study waiver for this new naproxen sodium drug product. The Clinical Division decided that for this new product, a waiver was granted for patients younger than 6 months old. However, the sponsor should conduct clinical studies in pediatric patients 6 months to 12 years old. The submission of the pediatric studies is deferred until February 18, 2009. When a pediatric program in the age group is undertaken, PK studies in pediatric patients are warranted to determine the appropriate dose recommendations for this patient population. Further, an age appropriate pediatric dosage form may need to be developed for the younger age group patients.

1.1 Recommendations

From a Clinical Pharmacology and Biopharmaceutics perspective, this application is acceptable.

1.2 Phase 4 Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings

In terms of clinical pharmacology and biopharmaceutics aspects, this application is supported by two pharmacokinetic studies (PRACS R03-725 and PRACS R03-739) and a comparative dissolution study (—04-264A). Individual study reviews are presented as appendices in Section 4 of this review.

Study PRACS R03-725 evaluated the bioequivalence of the test product with that of ALEVE tablets in healthy adults under fasting conditions. The data demonstrated that the estimated 90% confidence intervals (CIs) for log transformed C_{max} and AUC for the test product versus reference products in the fasting state were within the recommended limits (80-125%) (Table 2.5.1.1, Section 2.5). Therefore, the test product is bioequivalent to the reference product in adults under fasting conditions. The test product appeared to have slower absorption rate than the reference product (T_{max} of 1.42 hour vs. 0.99 hr). The analytical portion of this study was inspected by the Division of Scientific Investigation (DSI) and it was found that the data from the study are acceptable for Agency review.

Study PRACS R03-739 evaluated the bioequivalence of the test product and ALEVE tablets (the reference product) in healthy adults under fed state. The data from this study demonstrated that the estimated 90% confidence intervals for log transformed AUC for the test product versus the reference product was within the recommended limits (80-125%), but not for C_{max} (90% CI, 78.75, 94.16) (Table 2.5.1.2, Section 2.5). Similar to results from Study PRACS R03-725, the

test product had slower absorption rate than the reference product under fed conditions (T_{max} of 3.7 hr vs. 2.5 hr).

Food Effect

Food delayed the rate of absorption for both the test and the reference products, with a decrease in C_{max} and an increase in T_{max}. Overall extent of exposure, as indicated by AUC_{inf}, was similar between fasting and fed conditions (Tables 2.5.2.1 and 2.5.2.2, Section 2.5).

For the test product, naproxen sodium 220 mg soft gelatin capsules, C_{max} was 20% lower and T_{max} was 2.3 hr longer under fed conditions (Table 2.5.2.1, Section 2.5). AUC values of naproxen when administered with food were within 80-125% limits when compared to fasted conditions for the test product (Table 2.5.2.1, Section 2.5).

Similar food effect was also observed for the reference compound, ALEVE 220 mg tablets. Food decreases the rate of absorption of naproxen but not the extent of absorption for the reference compound. C_{max} was 15% lower and T_{max} was 1.5 hr longer under fed conditions (Table 2.5.2.2, Section 2.5). AUC values of naproxen when administered with food were within 80-125% limit when compared to fasted conditions for the reference compound (Table 2.5.2.2, Section 2.5).

Assessment of Delay in T_{max} of the Test Product

A delay in T_{max} for the test product relative to the reference product is observed under both fasting and fed conditions. In addition, food delays T_{max} for both the test and reference products. Whether the difference observed in mean T_{max} clinically meaningful is not clear. To relate plasma levels to potential clinical efficacy, the results from a dental pain model in the original ALEVE approval package (NDA 20-204) were used. In that model, the effective concentration for naproxen to achieve a meaningful pain reduction was 15,000 ng/mL.

Because a 440 mg dose of naproxen was used in Study PRACS R03-725 (fasting condition) and a 220 m g dose of naproxen was used in Study PRACS R03-739 (fed condition), and PK of naproxen was linear up to 500 mg, the plasma concentrations from Study PRACS R03-725 were divided by 2 to fit all data (fasting and fed) on the same plot (Figure 1). This PK profile also reflects the mean plasma levels for naproxen when one capsule is taken.

Under fasting conditions, both the test and reference products reached 15,000 naproxen plasma level before 30 min from the mean plasma-concentration profile (Figure 1). Therefore, the slightly-delayed absorption of naproxen from the test product to the reference product under fasting conditions (mean T_{max} of 1.42 hr vs. 0.99 hr) is most likely undetectable clinically.

Under fed conditions, it was found that the reference product reached level of 15,000 ng/mL before1 hour from the mean plasma-concentration profile (Figure 1). However, the test product did not reach this level until close to 1.5 to 2 hours (Figure 1). Compared to the fasting condition, the delayed absorption of naproxen from the test product under the fed condition may translate to delay of onset of analgesic effect which is not desirable clinically (mean T_{max} of 3.7 hour). In general, NSAID would be recommended to be taken with food due to GI effect.

However, in this case, food may delay the onset of analgesic effect. This finding would be brought to the attention of the Clinical Reviewer for labeling considerations.

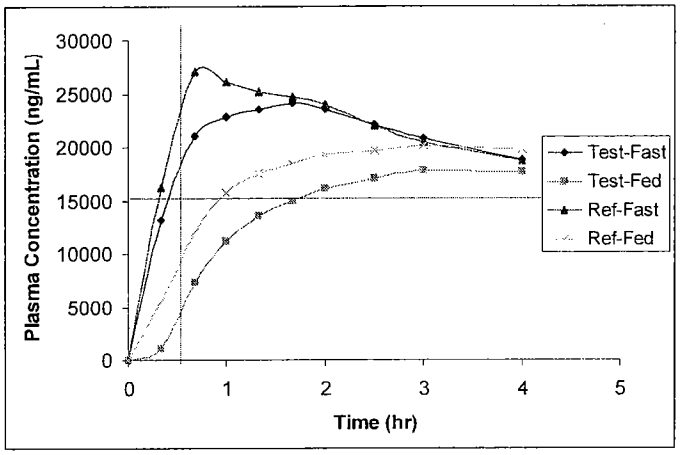

Figure 1. The mean plasma concentration-time profile (linear scale) for Test (♦) and Reference (■) products under fed and fasting conditions (0-4 hr).

Dissolution

The dissolution was performed and the samples were analyzed as per method [redacted]03-202 (see Table below). The lots of the test and reference products studied in bioequivalence studies were used in the dissolution study. Samples from 12 individual capsules or tablets from each lot were pulled and tested at 15, 30, 45, and 60 min. The dissolution profiles were compared with the similarity factor (f_2) calculations.

Apparatus	[redacted]
Speed	[redacted]
Number of units	[redacted]
Sampling times (minutes)	[redacted] and [redacted]
Media	[redacted]
Temperature	[redacted]
Analytical Method	HPLC [redacted]
Proposed Specification	Not less thar [redacted] (Q) is dissolved in 45 min

The test product has a slower dissolution rate than the reference product. On average, abou[redacted] of the test product was dissolved at 30 min while the reference product showed an almost complete dissolution at 30 min. The *in vitro* dissolution results were consistent with the results from the *in vivo* bioequivalence study that showed the test product had a slower absorption rate than the reference product.

A specification of [redacted](Q) at 45 min as proposed by the Sponsor for the test product is acceptable.

Lei Zhang, Ph.D.

Clinical Pharmacology Reviewer
Division of Clinical Pharmacology and Biopharmaceutics II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: _____

Suresh Doddapaneni, Ph.D.
Clinical Pharmacology Team Leader
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Office of Clinical Pharmacology and Biopharmaceutics

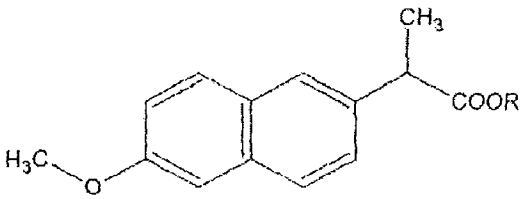
OCPB briefing (Optional Intra-Division) Date: January 27, 2006

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1.1. Physical-chemical Properties of Naproxen Sodium.

Drug Name	Naproxen Sodium
Chemical Name	(-)-6-methoxy-alpha-methyl-2-napthaleneacetic acid, sodium salt
Structure	 R = H (Naproxen); R = Na (Naproxen sodium)
Molecular Formula	$C_{14}H_{13}NaO_3$
Molecular Weight	252.23
Melting Point	225°C with decomposition
Appearance	White to creamy crystalline powder
Solubility	Soluble in water at neutral pH, soluble in methyl alcohol, sparingly soluble in alcohol, very slightly soluble in acetone, and practically insoluble in chloroform

The composition of the drug product (220 mg hard gelatin capsule) is listed in Table 2.1.1.2.

Table 2.1.1.2. Naproxen Sodium Liquid-filled Soft Gelatin Capsule Composition.

Component	mg/capsule
Capsule Fill	
Naproxen Sodium, USP	220
Lactic Acid, USP	[redacted]
Propylene Glycol, USP	
Povidone [redacted] USP	
Polyethylene Glycol [redacted], NF	
Total Fill Amount	[redacted]
Capsule Shell	
Gelatin, NF	DMF
Glycerin, USP	
Sorbitol [redacted]	
FD&C Blue #1	
FD&C Yellow #6	
Purified Water, USP	
Total Shell Weight	[redacted]

2.1.2 What is the proposed mechanism of drug action and therapeutic indications?

Naproxen sodium is a nonsteroidal anti-inflammatory drug (NSAID). It inhibits the synthesis of propstaglandins in body tissues by inhibiting cyclooxygenases. At least 2 isoenzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), have been identified that catalyze the formation of postglandins in the arachidonic acid pathway. Naproxen inhibits both COX-1 and COX-2. Although the exact mechanisms have not been clearly established, NSAIDs appear to exert anti-inflammatory, analgesic, and antipyretic activity principally through inhibition of the COX-2 isoenzyme; COX-1 inhibition presumably is responsible for the drugs' unwanted effects on GI mucosa and platelet aggregation.

This is a 505 (b)(2) application. The proposed indication is the same as the reference product, ALEVE tablets, i.e., fever reduction and temporary relief from aches and pains for the common cold, headache, toothace, muscle ache, backache, minor arthritis pain and menstrual cramps for adults and children 12 years and older.

2.1.3 What is the proposed dosage and route of administration of naproxen sodium?

Naproxen sodium capsules are taken orally. The following is extracted from the proposed labeling:

2.2 General Clinical Pharmacology

2.2.1 What is known about the PK characteristics for naproxen in general?

Naproxen sodium is completely absorbed from the GI tract. Oral bioavailability of naproxen is approximately 95%. The peak plasma concentrations occur in 1-2 hours following oral absorption of naproxen sodium. The volume of distribution is 0.16 L/kg. Plasma half-life ranges from 10-20 hours (mean of 13 hr). At therapeutic doses, naproxen is more than 99% bound to plasma proteins.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes, total naproxen concentrations were measured in human plasma. Please refer to Section 2.6 Analysis for analytical details.

2.2.3 What are the PK characteristics of the drug? How do they compare to those of the RLD (ALEVE tablets, 220 mg)?

Fasting conditions (Study PRACS R03-725):

The PK parameters for Test and Reference products under fasting conditions were summarized in Table 2.2.3.1.

Table 2.2.3.1. Summary of PK Parameters for Test and Reference Products under Fasting Conditions (N=24, Dose=440 mg).

Parameters	Test		Reference	
	Mean	CV	Mean	CV
AUC_{0-t} (ng·hr/mL)	782232	15.4	773444	20.0
AUC_{inf} (ng·hr/mL)	830462	16.4	830822	20.8
C_{max} (ng/mL)	53625	19.1	57210	12.6
T_{max} (hr)	1.42	55.5	0.99	47.1
K_{elim} (hr^{-1})	0.038	12.4	0.039	16.7
$T_{1/2}$ (hr)	18.5	13.9	18.5	18.6

The median T_{max} was 1.33 hr for the Test (range 0.33-3 hr, 1.42 ± 0.79, mean ± SD, N=24) and 0.67 hr for the Reference (range 0.33-2 hr, 0.99 ± 0.47, mean ± SD, N=24) products, respectively under fasting conditions.

Fed conditions (Study PRACS R03-739):
The PK parameters for Test and Reference products under fed (non-fasting) conditions were summarized in Table 2.2.3.2.

Table 2.2.3.2. Summary of PK Parameters for Test and Reference Products under Fed Conditions (N=27, Dose=220 mg).

Parameters	Test		Reference	
	Mean	CV	Mean	CV
AUC_{0-t} (ng·hr/mL)	407136	19.2	415316	19.5
AUC_{inf} (ng·hr/mL)	444744	19.8	451526	19.9
C_{max} (ng/mL)	21719	28.6	24499	18.1
T_{max} (hr)	3.7	78.7	2.5	63.2
K_{elim} (hr^{-1})	0.039	22.8	0.038	22
$T_{1/2}$ (hr)	18.6	21	19.1	24.2

The median T_{max} was 3 hr for the Test (range 1-12 hr, 3.7 ± 2.9, mean ± SD, N=27) and 2 hr for the Reference (range 0.67-8 hr, 2.5 ± 1.6, mean ± SD, N=27) products, respectively under non-fasting conditions.

2.3 Intrinsic Factors

Not applicable.

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

2.5.1 Is naproxen sodium liquid-filled soft gelatin capsules (220 mg) bioequivalent to the RLD (ALEVE tablets, 220 mg)) under fasting and fed conditions in healthy adults?

Study PRACS R03-725 evaluated the bioequivalence of the test product with that of ALEVE tablets in healthy adults under fasting conditions. The data demonstrated that the estimated 90% confidence intervals (CIs) for log transformed C_{max} and AUC for the test product versus reference products in the fasting state were within the acceptable limits (80-125%) (Table 2.5.1.1). Therefore, the test product is bioequivalent to the reference product in adults under fasting conditions. The test product appeared to have slower absorption rate than the reference product (T_{max} of 1.42 hour vs. 0.99 hr). The analytical portion of this study was inspected by the Division of Scientific Investigation (DSI) and it was found that the data from the study are acceptable for Agency review.

Table 2.5.1.1. Comparison of Geometric Least Squares Means of C_{max}, AUC_{0-2}, AUC_{0-4}, AUC_{0-t}, and AUC_{inf} for Test and Reference Products under Fasting Conditions.

Naproxen	C_{max}	AUC_{0-2}	AUC_{0-4}	AUC_{0-t}	AUC_{inf}
Test Product Geometric Mean	52620	743099	1590499	773412	819861
Reference Product Geometric Mean	56739	867389	1698359	758909	814286
% Ratio	92.74	85.67	93.65	101.91	100.68
90% Confidence Interval	(87.79, 97.97)	(78.30, 93.73)	(90.06, 97.38)	(98.09, 105.88)	(97.99, 103.45)

Study PRACS R03-739 evaluated the bioequivalence of the test product and ALEVE tablets (the reference product) in healthy adults under fed states. The data from this study demonstrated that the estimated 90% confidence intervals for log transformed AUC for the test product versus the

reference product was within the acceptable limits (80-125%), but not for C_{max} (90% CI, 78.75, 94.16) (Table 2.5.1.2). Similar to results from Study R03-725, the test product had slower absorption rate than reference product under fed conditions (T_{max} of 3.7 hr vs. 2.5 hr). Partial AUC values of early timepoints (e.g., 0-2 hr and 0-4 hr) were not bioequivalent between the test and the reference products with the test product being lower.

Table 2.5.1.2. Comparison of Geometric Least Squares Means of C_{max}, AUC_{0-2}, AUC_{0-4}, AUC_{0-t}, and AUC_{inf} for Test and Reference Products under Fed Conditions.

Naproxen	C_{max}	AUC_{0-2}	AUC_{0-4}	AUC_{0-t}	AUC_{inf}
Test Product Geometric Mean	20821	110791	443781	4039491	441040
Reference Product Geometric Mean	24178	22211	630951	411049	446755
% Ratio	86.11	49.88	70.34	98.27	98.72
90% Confidence Interval	(78.75, 94.16)	(34.45, 72.23)	(56.69, 87.27)	(96.23, 100.36)	(96.39, 101.11)

2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?

Food delayed the rate of absorption for both the test and the reference products, with a decrease in C_{max} and an increase in T_{max}. Overall extent of exposure, as indicated by AUC_{inf}, was bioequivalent between fasting and fed conditions.

For the test product, naproxen sodium 220 mg soft gelatin capsules, C_{max} was 20% lower and T_{max} was 2.3 hr longer under fed conditions (Table 2.5.2.1). AUC values of naproxen when administered with food were within 80-125% limit when compared to fasted conditions for the test product (Table 2.5.2.1).

Table 2.5.2.1. Comparisons of Naproxen Results for 220 mg Naproxen Sodium Soft Gelatin Capsules When Administered as a Single Dose after a Standard High-Fat Breakfast (Test-Fed) and When Administered After an Overnight Fast (Test-Fasted)*.

	Geometric Least Squares Means			90% Confidence Interval	
Parameter	Test-Fed	Test-Fasted	Ratio [1]	Lower	Upper
AUC_{0-t} (ng·hr/mL)	399393	385764	103.53	94.84	113.02
AUC_{inf} (ng·hr/mL)	435708	409107	106.50	97.18	116.72
C_{max} (ng/mL)	20779	26295	79.02	69.50	89.85
T_{max} (hr) [2]	3.7	1.4	-	-	-

* Data for fasted conditions were divided by 2 assuming linear PK between 220 mg and 440 mg.

[1] Ratio calculated as Fed to Fasted.
[2] Arithmetic mean

Similar food effect was also observed for the reference compound, ALEVE 220 mg tablets. Food decreases the rate of absorption of naproxen but not the extent of absorption for the reference compound. C_{max} was 15% lower and T_{max} was 1.5 hr longer under fed conditions (Table 2.5.2.2). AUC values of naproxen when administered with food were within 80-125% limit when compared to fasted conditions for the reference product (Table 2.5.2.2).

Table 2.5.2.2. Comparisons of Naproxen Results for 220 mg ALEVE Tablets When Administered as a Single Dose after a Standard High-Fat Breakfast (Ref-Fed) and When Administered After an Overnight Fast (Ref-Fasted)*.

	Geometric Least Squares Means			90% Confidence Interval	
Parameter	Ref-Fed	Ref-Fasted	Ratio [1]	Lower	Upper
AUC_{0-t} (ng·hr/mL)	407318	379455	107.34	97.62	118.03
AUC_{inf} (ng·hr/mL)	442461	407143	108.67	98.61	119.77
C_{max} (ng/mL)	24063	28369	84.82	78.20	92.00
T_{max} (hr) [2]	2.5	0.99	-	-	-

* Data for fasted conditions were divided by 2 assuming linear PK between 220 mg and 440 mg.
[1] Ratio calculated as Fed to Fasted.
[2] Arithmetic mean

2.5.3 How do the dissolution profiles of the test product compared to the reference prouduct? How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

The dissolution was performed and the samples were analyzed as per method [redacted]03-202 (see Table below). The lots of the test and reference products studied in bioequivalence studies were used in the dissolution study. Samples from 12 individual capsules or tablets from each lot were pulled and tested at 15, 30, 45, and 60 min.

Apparatus	[redacted]
Speed	[redacted]
Number of units	[redacted]
Sampling times (minutes)	[redacted]
Media	[redacted]
Temperature	[redacted]
Analytical Method	HPLC [redacted]
Proposed Specification	Not less than [redacted] (Q) is dissolved in 45 min

The test product has a slower dissolution rate than the reference product (Figure 2.5.3.1). On average, about [redacted] of the test product was dissolved at 30 min while the reference product

showed a complete dissolution at 30 min. The *in vitro* dissolution results were consistent with the results from the in vivo bioequivalence study that showed the test product had a slower absorption rate than the reference product.

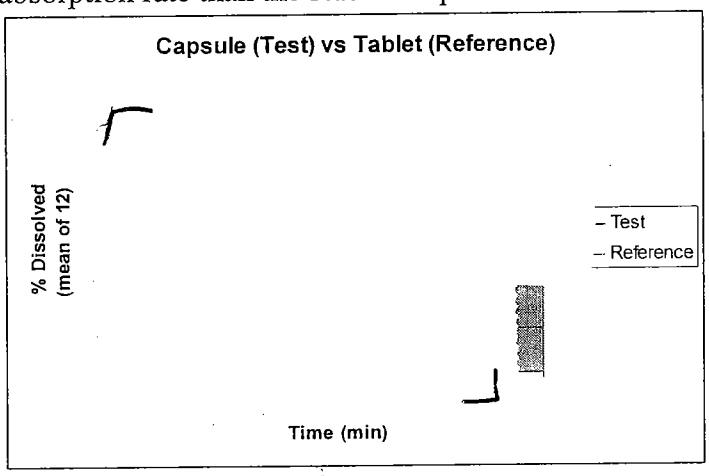


Figure 2.5.3.1. Comparative Dissolution Profiles between the Test and Reference Products.

Based on the dissolution profile of the test product, a specification of [redacted] (Q) at 45 min as proposed by the Sponsor for the test product is acceptable.

2.6 Analytical

2.6.1 Were the analytical methods used to determine naproxen in biological fluids adequately validated?

Yes. Plasma samples were analyzed by a validated HPLC method ([redacted]) [redacted] by the PRACS Institute, Ltd., Bioanalytical Laboratory as summarized in Table 2.6.1.1. The standard naproxen (Lot 072K1806) and internal standard (IS) [redacted] (Lot 043K0684) were supplied by [redacted] as performed on naproxen to IS peak response ratio versus [redacted] The lower limit of quantitation (LOQ) was [redacted] ng/mL.

Table 2.6.1.1. Analytical Assay Used for Naproxen.

Assay Method	[redacted]
Analytical Site	[redacted]
Internal Standard	[redacted]
Matrix	[redacted]
Accuracy (% Bias) *Within-batch*	[redacted]
Precision (CV%) *Within-batch*	[redacted]
Accuracy (% Bias) *Between-batch*	[redacted]

Precision (CV%) *Between-batch*	[redacted]
Standard Curve Range	[redacted] ng/mL (R^2 > [redacted])
QCs	[redacted] ng/mL and one blind QC ([redacted] ng/mL)
Sensitivity (LOQ)	[redacted] ng/mL
Recovery	Naproxen: [redacted] IS: [redacted]
Selectivity	No significant baseline interference was detected at the retention time of Naproxen or internal standard.
Stability	Freeze/thraw: [redacted] Long term: [redacted]

3 LABELING RECOMMENDATIONS

The label for an OTC product does not contain PK information. Please refer to the appropriate reviews from ONP/DNCE for details of labeling review comments.

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APPENDICES

3.1 Proposed Package Inserts from the Sponsor

Proposed Carton Label Text

3.2 Individual Study Review

3.2.1 PRACS Protocol No. R03-725: A Relative Bioavailability Study of 220 mg Naproxen Sodium Soft Gelatin Capsules under Fasting Conditions

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Objective: To evaluate the relative bioavailability (rate and extent of absorption) of the test Naproxen Sodium Capsules 220 mg (liquid-filled soft gelatin capsules) compared to the reference ALEVE Tablets 220 mg after a single oral dose administration of 440 mg (2 X 220 mg) under fasting conditions in healthy adults.

(Reviewer's Comment: Although the 440 mg dose is included in the OTC label, Agency generally prefers the use of a 220 mg dose (a single tablet/liquid-filled capsule) to assess in vivo bioequivalence. Because multiple dose units may result in multiple peaking which could translate into a peak plasma level value that does not support bioequivalence with the reference list drug. This comment was conveyed to the Sponsor during the IND phase but the Sponsor had initiated the protocol already.)

Study Site: PRACS Institute, Ltd., Fargo, North Dakota 58104

Principle Investigator: James D. Carlson, Pharm.D.

Study Periods: Period I: December 4 to December 7, 2004
Period II: December 18 to December 21, 2004

Analytical Site: PRACS Institute, Ltd., 4801 Amber Valley Parkway, Fargo, North Dakota 58104

Analysis Dates: December 22, 2004 to January 2, 2005

Study Design: This was a randomized, single dose, two-way crossover study in 28 healthy subjects (9 males and 19 females) under fasting conditions (Table 1 and Table A1, Appendix). Twenty-seven subjects finished the study. Subject 14 was dropped from the study prior to Period II dose administration due to a positive pregnancy screen. Subject 21 failed to return for the Period II ambulatory blood sample collections.

Subjects received the two treatments separated by a 14-day washout period. Treatment A (test product) was Naproxen Sodium Capsules 220 mg (liquid-filled soft gelatin capsules) and Treatment B (reference product) was ALEVE® Tablets 220 mg (Bayer). A single dose of 440 mg (2 X 220 mg) was administered with 240 mL of room temperature water after an overnight fast.

Table 2. Summary of PK Parameters for Test and Reference Products under Fasting Conditions (N=24).

Parameters	Test		Reference	
	Mean	CV	Mean	CV
AUC_{0-t} (ng·hr/mL)	782232	15.4	773444	20.0
AUC_{inf} (ng·hr/mL)	830462	16.4	830822	20.8
C_{max} (ng/mL)	53625	19.1	57210	12.6
T_{max} (hr)	1.42	55.5	0.99	47.1
K_{elim} (hr^{-1})	0.038	12.4	0.039	16.7
$T_{1/2}$ (hr)	18.5	13.9	18.5	18.6

The 90% confidence interval (CI) of the relative geometric mean of the Test to the Reference product for C_{max}, AUC_{0-4}, AUC_{0-t}, and AUC_{inf} were all within the acceptance range of 80-125% under the fasting conditions (Table 3). However, when partial AUC of 0-2 hours were compared between the Test and the Reference compound, the lower boundary of 90% CI was slightly below 80 (78.3).

Table 3. Comparison of Geometric Least Squares Means of C_{max}, AUC_{0-2}, AUC_{0-4}, AUC_{0-t}, and AUC_{inf} for Test and Reference Products under Fasting Conditions.

Naproxen	C_{max}	AUC_{0-2}	AUC_{0-4}	AUC_{0-t}	AUC_{inf}
Test Product Geometric Mean	52620	743099	1590499	773412	819861
Reference Product Geometric Mean	56739	867389	1698359	758909	814286
% Ratio	92.74	85.67	93.65	101.91	100.68
90% Confidence Interval	(87.79, 97.97)	(78.30, 93.73)	(90.06, 97.38)	(98.09, 105.88)	(97.99, 103.45)

The median T_{max} was 1.33 hr for the Test (range 0.33-3 hr, 1.42 ± 0.79, mean ± SD, N=24) and 0.67 hr for the Reference (range 0.33-2 hr, 0.99 ± 0.47, mean ± SD, N=24) products, respectively. Stick plot of the individual T_{max} values was shown in Figure 2. Distribution of individual T_{max} values was shown in Figure 3. T_{max} values were variable among subjects, especially for the Test product.

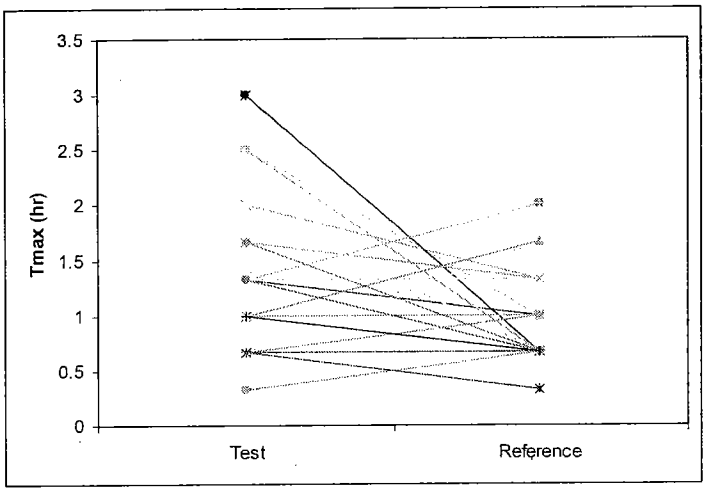

Figure 2. Stick plot of the individual T_{max} values of Test and Reference products under fasting conditions.

Discussion: To relate plasma levels to potential clinical efficacy, the results from a dental pain model in the original ALEVE approval package (NDA 20-204) were used. In that model, the effective concentration for naproxen to achieve a meaningful pain reduction was 15,000 ng/mL. Because a 440 mg dose of naproxen was used in this study, and PK of naproxen was linear up to 500 mg, the time to reach the effective concentration of 15,000 ng/mL at a 220 mg dose under fasting conditions was estimated by determining the time to reach the concentration of 30,000 ng/mL from the mean plasma-concentration profile for both the test and reference naproxen products at a 440 mg dose of naproxen from this study (Figure 3). It was found that both the test and reference products reached 30,000 ng/mL before 30 min. Therefore, the delayed absorption of naproxen from the test product compared to that from the reference product (mean T_{max} of 1.42 hr vs. 0.99 hr) is most likely undetectable clinically.

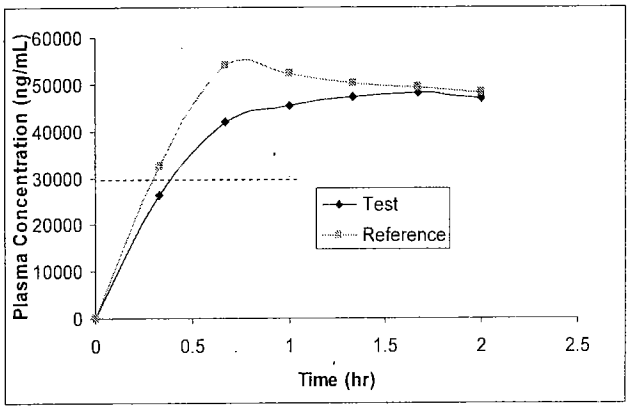

Figure 4. The mean plasma concentration-time profile (N=24, linear scale) for Test (♦) and Reference (■) products under fasting conditions (0-2 hr).

Conclusions: The 90% confidence interval of the relative geometric mean of the Test (naproxen sodium soft gelatin capsule) to the Reference product (ALEVE tablet) for C_{max}, AUC_{0-t}, and AUC_{inf} were within the acceptance range of 80-125% under the fasting conditions. Therefore, the test product is bioequivalent to the reference product. The Test product appeared to have slower absorption rate than the Reference product. Because the Test product likely reached the effective

concentration before 30 min as the Reference product, the difference in absorption rate (or T_{max}) is not considered clinically-detectable.

Appendix.
Table A1. Demographic Data (Study R03-725).

Subject			Demographic Data						
Number	Initials	Chart	Age	Weight (lb)	Height (in)	BMI	Body Frame	Gender	Race
01		163965	52	167	64	28.7	Medium	Female	Caucasian
02		95825	61	137	63	24.3	Medium	Female	Caucasian
03		102407	29	156	62	28.5	Large	Female	Caucasian
04		116958	20	171	70	24.5	Medium	Male	Caucasian
05		95748	29	236	73	31.2	Large	Male	Caucasian
06		104253	22	169	70	24.3	Medium	Male	Caucasian
07		116663	33	186	70	26.7	Medium	Male	Caucasian
08		104235	31	151	67	23.7	Medium	Female	Caucasian
09		116095	21	168	70	24.1	Medium	Male	Caucasian
10		165583	26	165	64	28.3	Medium	Female	Caucasian
11		97998	26	119	64	20.4	Medium	Female	Caucasian
12		106695	22	165	67	25.9	Small	Male	Caucasian
13		118108	23	178	69	26.3	Medium	Male	Hispanic
14		165564	19	163	66	26.3	Medium	Female	Black
15		163586	18	128	64	22.0	Medium	Female	Caucasian
16		165565	56	145	67	22.7	Medium	Female	Caucasian
17		104061	52	160	63	28.4	Large	Female	Caucasian
18		99752	24	177	69	26.2	Medium	Male	Caucasian
19		116461	55	173	64	29.7	Medium	Female	Caucasian
20		163286	66	167	65	27.8	Large	Female	Caucasian
21		101361	22	163	66	26.3	Medium	Male	Caucasian
22		165587	18	119	63	21.1	Medium	Female	Caucasian
23		116724	22	131	63	23.2	Medium	Female	Caucasian
24		118470	46	151	67	23.7	Medium	Female	Caucasian
25		108428	43	150	63	26.6	Medium	Female	Caucasian
26		165582	18	153	61	29.0	Medium	Female	Caucasian
27		165584	51	166	63	29.5	Medium	Female	Caucasian
28		108196	52	180	67	28.2	Large	Female	Caucasian

3.2.2 PRACS Protocol No. R03-739: A Relative Bioavailability Study of 220 mg Naproxen Sodium Soft Gelatin Capsules under Non-Fasting Conditions

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Objective: To evaluate the relative bioavailability (rate and extent of absorption) of the test Naproxen Sodium Capsules 220 mg (liquid-filled soft gelatin capsules) compared to the reference ALEVE Tablets 220 mg after a single oral dose administration of 220 mg under non-fasting conditions in healthy adults.

Study Site: PRACS Institute, Ltd., Fargo, North Dakota 58104

Principle Investigator: James D. Carlson, Pharm.D.

Study Periods: Period I: February 13-16, 2005
Period II: February 27-March 2, 2005

Analytical Site: PRACS Institute, Ltd., 4801 Amber Valley Parkway, Fargo, North Dakota 58104

Analysis Dates: March 3-9, 2005

Study Design: This was a randomized, single dose, two-way crossover study in 30 healthy subjects (11 males and 19 females) under non-fasting conditions (Table 1 and Table A1, Appendix). Twenty-nine subjects finished the study. Subject 12 elected to withdraw prior to Period II due to a family emergency.

Table 1. Demographic Summary.

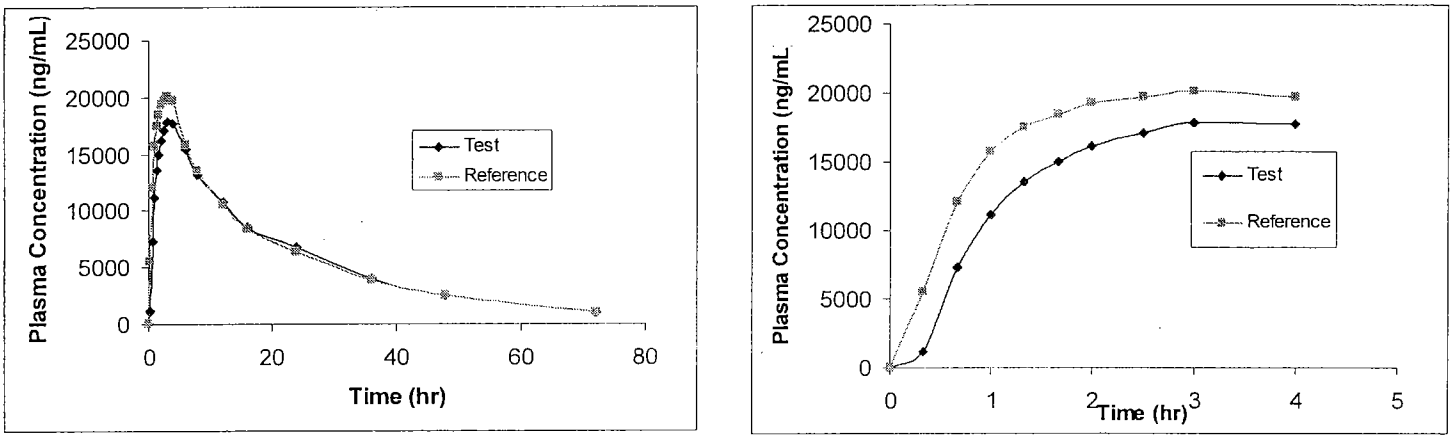
All Subjects	Age (yr)	Weight (lb)	Height (in)	BMI
N	30	30	30	30
Mean	21.0	155.7	67.6	23.9
Std. Dev.	2.5	24.3	3.2	2.7
Median	21	154.5	67.0	24.1
Minimum	18	111.0	62.0	18.8
Maximum	30	216.0	74.0	29.8
Range	12	105.0	12.0	11.0

Subjects received the two treatments separated by a 14-day washout period. Treatment A (test product) was Naproxen Sodium Capsules 220 mg (liquid-filled soft gelatin capsules) and Treatment B (reference product) was ALEVE® Tablets 220 mg (Bayer). Subjects were dosed 30

Pharmacokinetic Results:

Overall Profile

Figure 1 demonstrates the mean plasma concentration-time profile (linear scale) for Test (naproxen sodium 220 mg capsules) and Reference (ALEVE 220 mg tablets) products under fed conditions. The graph was also expanded to show the early timepoints (0-4 hour). The test product in general showed lower C_{max} and longer T_{max} compared to the reference product under fed conditions.



(a) 0-72 hr **(b) 0-4 hr**

Figure 1. Plasma concentration-time profile (N=27, linear scale) for Test (♦) and Reference (■) products under fed conditions.

Test vs Reference under Fed Conditions

The PK parameters (C_{max}, T_{max}, AUC_{0-t}, AUC_{inf}) for Test and Reference products under fed conditions were summarized in Table 2.

Table 2. Summary of PK Parameters for Test and Reference Products under Fed Conditions (N=27).

Parameters	Test		Reference	
	Mean	CV	Mean	CV
AUC_{0-t} (ng·hr/mL)	407136	19.2	415316	19.5
AUC_{inf} (ng·hr/mL)	444744	19.8	451526	19.9
C_{max} (ng/mL)	21719	28.6	24499	18.1
T_{max} (hr)	3.7	78.7	2.5	63.2
K_{elim} (hr^{-1})	0.039	22.8	0.038	22
$T_{1/2}$ (hr)	18.6	21	19.1	24.2

The 90% confidence interval (CI) of the relative geometric mean of the Test to the Reference product for AUC_{0-t} and AUC_{inf} were within the acceptance range of 80-125% under the fed conditions (Table 3). However, the relative geometric mean of the Test to the Reference product for C_{max} were not within the acceptance range of 80-125%. Cmax for the test product is slightly lower (14% lower). A delay in absorption for the test product is evident that partial AUC of 0-2 hours and 0-4 hours were all lower than the reference product, the lower boundary of 90% CI was below 80 (34.45 and 56.69, respectively).

Table 3. Comparison of Geometric Least Squares Means of C_{max}, AUC_{0-2}, AUC_{0-4}, AUC_{0-t}, and AUC_{inf} for Test and Reference Products under Fed Conditions.

Naproxen	C_{max}	AUC_{0-2}	AUC_{0-4}	AUC_{0-t}	AUC_{inf}
Test Product Geometric Mean	20821	110791	443781	4039491	441040
Reference Product Geometric Mean	24178	22211	630951	411049	446755
% Ratio	86.11	49.88	70.34	98.27	98.72
90% Confidence Interval	(78.75, 94.16)	(34.45, 72.23)	(56.69, 87.27)	(96.23, 100.36)	(96.39, 101.11)

The median T_{max} was 3 hr for the Test (range 1-12 hr, 3.7 ± 2.9, mean ± SD, N=27) and 2 hr for the Reference (range 0.67-8 hr, 2.5 ± 1.6, mean ± SD, N=27) products, respectively under non-fasting conditions. Stick plot of the individual T_{max} values was shown in Figure 2. As of note, two subjects (Subjects 16 and 30) in the test arm had a Tmax of 12 hr. If excluding these 2 subjects, mean T_{max} would be 3.0 hr for the Test product.

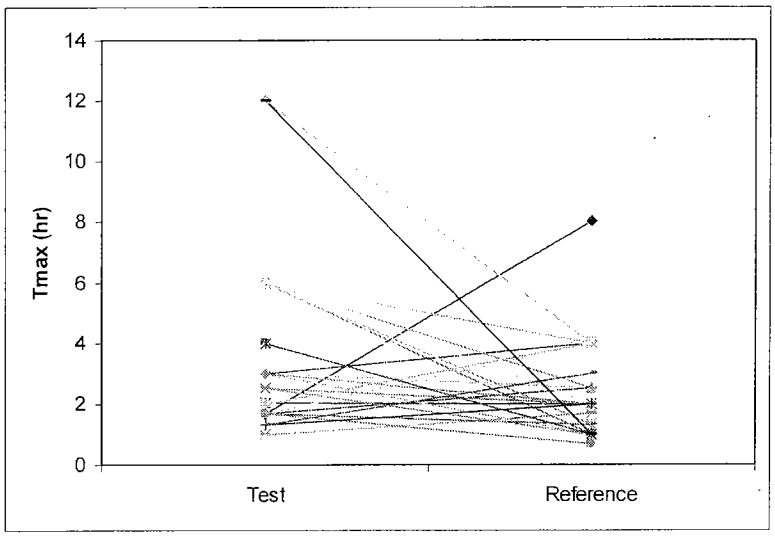


Figure 2. Stick plot of the individual T_{max} values of Test and Reference products under fed conditions.

Discussion: The data from the original ALEVE approval package (NDA 20-204) indicated an effective concentration of 15,000 ng/mL for naproxen (at a 220 mg dose) to achieve a meaningful pain reduction. The time to reach the effective concentration of 15,000 ng/mL was estimated from the mean plasma-concentration profile for both the test and reference naproxen products from this study (Figure 3). It was found that the reference product reached this level before1 hour. However, the test product did not reach this level until close to 1.5 to 2 hours. The delayed absorption of naproxen from the test product under the fed condition may translate to delay of onset of analgesic effect which is not desirable clinically (mean T_{max} of 3.7 hours). This would be brought to the attention of the Clinical Reviewer for labeling considerations.

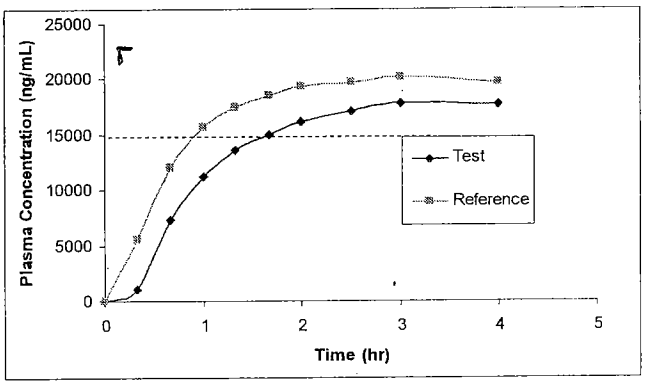


Figure 3. The mean plasma concentration-time profile (N=24, linear scale) for Test (♦) and Reference (▩) products under fed conditions (0-4 hr).

Conclusions: The 90% confidence interval of the relative geometric mean of the Test (naproxen soft gelatin capsule) to the Reference product (ALEVE tablet) for AUC_{0-t} and AUC_{inf} were within the acceptance range of 80-125% under the fed conditions. However, C_{max} for the test product is slightly lower (14% lower) compared to the reference product under fed conditions, the relative geometric mean of the Test to the Reference product for C_{max} were not within the acceptance range of 80-125%. Furthermore, the Test product appears to have slower absorption rate than the Reference product under fed condition. Whether the difference in absorption is clinically meaningful is not clear. Based on one dental pain model, it may not be desirable clinically because the test product did not reach the effective concentration of 15,000 ng/mL until close to 1.5 to 2 hours at a dose of 220 mg based on the mean plasma-concentration time profile.

Appendix.
Table A1. Demographic Data (Study R03-739).

Subject			Demographic Data						
Number	Initials	Chart	Age	Weight (lb)	Height (in)	BMI	Body Frame	Gender	Race
01	[illegible]	165592	22	186	68	28.3	Large	Female	Caucasian
02		98646	27	216	74	27.8	Medium	Male	Caucasian
03		112939	30	147	64	25.2	Medium	Female	Caucasian
04		166296	19	132	67	20.7	Medium	Female	Caucasian
05		162734	22	150	63	26.6	Medium	Female	Caucasian
06		166311	18	111	64	19.1	Medium	Female	Caucasian
07		164736	19	169	72	22.9	Medium	Male	Caucasian
08		116760	21	117	62	21.4	Medium	Female	Caucasian
09		163675	20	159	66	25.7	Medium	Female	Caucasian
10		116928	24	194	72	26.3	Large	Male	Caucasian
11		106505	22	129	65	21.5	Small	Male	Caucasian
12		116015	21	150	66	24.2	Medium	Female	Caucasian
13		161489	19	127	69	18.8	Medium	Female	Caucasian
14		102514	23	179	65	29.8	Large	Female	Caucasian
15		116129	20	182	73	24.0	Medium	Male	Caucasian
16		102279	22	162	69	23.9	Large	Female	Caucasian
17		166372	21	126	65	21.0	Medium	Female	Caucasian
18		118883	19	158	67	24.8	Medium	Female	Caucasian
19		109536	19	151	66	24.4	Medium	Male	Caucasian
20		162133	21	148	68	22.5	Medium	Female	Caucasian
21		162266	22	147	69	21.7	Medium	Female	Caucasian
22		118781	22	171	68	26.0	Medium	Male	Caucasian
23		112320	21	167	70	24.0	Medium	Male	Caucasian
24		116373	19	129	67	20.2	Medium	Female	Caucasian
25		166402	19	175	69	25.9	Medium	Female	Caucasian
26		161205	19	177	73	23.4	Medium	Male	Caucasian
27		166411	19	160	67	25.1	Medium	Male	Caucasian
28		166468	21	133	65	22.2	Medium	Female	Caucasian
29		114131	21	147	63	26.1	Medium	Female	Caucasian
30	[illegible]	166409	19	173	71	24.1	Medium	Male	Caucasian

4.2.3 Dissolution Profile Testing Study

Doc No. PD04-264A: Report for Comparative Dissolution of Banner Pharmacaps Naproxen Sodium Soft Gelatin Capsules versus Aleve Naproxen Sodium Tablets

Objective: To compare the dissolution profiles of a lot of naproxen sodium capsules (test, Lot XPP0309006B) to a lot of Aleve naproxen sodium tablets (reference, Lot 273503J).

Methods: The dissolution was performed and the samples were analyzed as per method — 03-202 (see Table below). The lots of the test and reference products studied in bioequivalence studies were used in the dissolution study. Samples from 12 individual capsules or tablets from each lot were pulled and tested at 15, 30, 45, and 60 min. The dissolution profiles were compared with the similarity factor (f_2) calculations. An f_2 value between 50 and 100 indicates the two dissolution profiles are similar.

Apparatus	
Speed	
Number of units	
Sampling times (minutes)	
Media	
Temperature	37 ± 0.5 °C
Analytical Method	HPLC
Proposed Specification	Not less than —) is dissolved in 45 min

Results:

1. Dissolution Results for the Test Product (Lot XPP0309006B)

Banner Capsules

Vessel	Time	(minutes)		
#	15	30	45	60
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
average	59	77	88	92
sd	28.6	13.0	9.1	6.6
rsd				
range				

2. Dissolution Results for the Reference Product (Lot 273503J)

Aleve Tablets

Vessel #	Time (minutes) 15	30	45	60
1	[redacted]	[redacted]	[redacted]	[redacted]
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12	[redacted]	[redacted]	[redacted]	[redacted]
average	95	101	101	101
sd	11.2	1.2	1.0	1.0
rsd	[redacted]	[redacted]	[redacted]	[redacted]
range	[redacted]	[redacted]	[redacted]	[redacted]

3. Comparative Dissolution Profiles

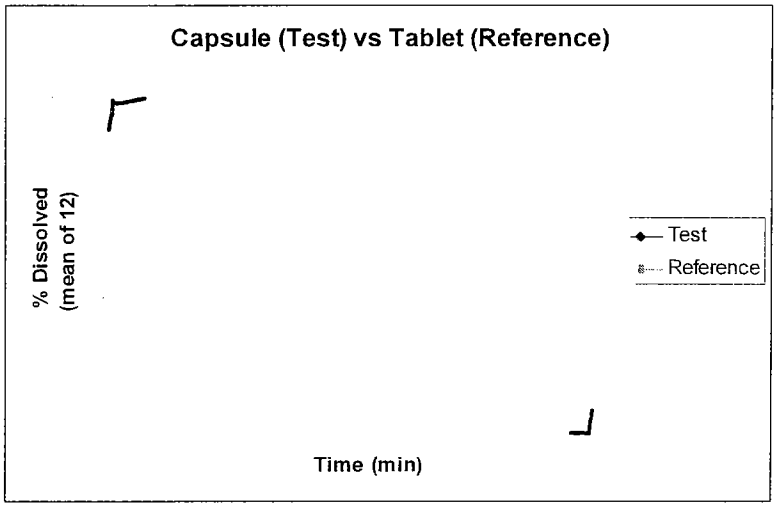


Figure 1. Comparative Dissolution Profiles between the Test and Reference Products.

4. f_2 Calculations

Conclusions: The test product has a slower dissolution rate than the reference product. On average, about —% of the test product was dissolved at 30 min while the reference product showed an almost complete dissolution at 30 min. The *in vitro* dissolution results were consistent with the results from the *in vivo* bioequivalence study that showed the test product had a slower absorption rate than the reference product.

A specification of —% (Q) at 45 min as proposed by the Sponsor for the test product is acceptable.

APPEARS THIS WAY
ON ORIGINAL

3.3 OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-920	Brand Name	N/A
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Naproxen Sodium
Medical Division	OTC (HFD-560)	Drug Class	NSAID
OCPB Reviewer	Lei Zhang, Ph.D.	*Indication(s)*	OTC use for temporarily relieves minor aches and pains due to: headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, menstrual cramps, and temporarily reduces fever
OCPB Team Leader	Dennis Bashaw, Pharm. D.	Dosage Form	Liquid-filled Soft Gelatin Capsules, 220 mg
		Dosing Regimen	adults and children 12 years and older: • take 1 capsule every 8 to 12 hours while symptoms last • for the first dose you may take 2 capsules within the first hour • the smallest effective dose should be used • do not exceed 2 capsules in *any* 8- to 12-hour period • do not exceed 3 capsules in a 24 hour period children under 12 years: • ask a doctor
Date of Submission	4/15/2005	Route of Administration	PO
Estimated Due Date of OCPB Review	12/20/2005	Sponsor	Banner Pharmacaps, Inc.
PDUFA Due Date	2/18/2006	Priority Classification	3-S
Division Due Date		Relevant IND	IND 71,161

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
Human PK Summary	X			
Labeling	X			

Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		**RLD: Aleve tablets PRACS Protocol No. R03-725**
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1		**Comparative dissolution with Aleve Doc No 04-264A**
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			**Ask for waiver for pediatric patients age 12 year and below**
Literature References	X			
Total Number of Studies		2		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm ?	X	
QBR questions (key issues to be considered)	• Is the new formulation of naproxen soft gelatin capsule bioequivalent to the reference listing drug, Aleve, under the fasting condition in adults? • What is the food effect of this new dosage form?	
Other comments or information not included above		
Primary reviewer Signature and Date	Lei Zhang, 6/7/2005	
Secondary reviewer Signature and Date	Dennis Bashaw, 6/7/2005	

CC: NDA 21-920, HFD-850 (P. Lee), HFD-560 (Shay), HFD-880 (L. Zhang, Bashaw, Lazor, Selen), CDR

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lei K Zhang
2/1/2006 11:48:59 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
2/1/2006 12:38:23 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-920**	**Brand Name**	**N/A**
OCPB Division (I, II, III)	**DPE III (HFD-880)**	**Generic Name**	**Naproxen Sodium**
Medical Division	**OTC (HFD-560)**	**Drug Class**	**NSAID**
OCPB Reviewer	**Lei Zhang, Ph.D.**	**Indication(s)**	**OTC use for temporarily relieves minor aches and pains due to: headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, menstrual cramps, and temporarily reduces fever**
OCPB Team Leader	**Dennis Bashaw, Pharm. D.**	**Dosage Form**	**Liquid-filled Soft Gelatin Capsules, 220 mg**
		Dosing Regimen	adults and children 12 years and older: • take 1 capsule every 8 to 12 hours while symptoms last • for the first dose you may take 2 capsules within the first hour • the smallest effective dose should be used • do not exceed 2 capsules in any 8- to 12-hour period • do not exceed 3 capsules in a 24 hour period children under 12 years: • ask a doctor
Date of Submission	**4/15/2005**	**Route of Administration**	**PO**
Estimated Due Date of OCPB Review	**12/20/2005**	**Sponsor**	**Banner Pharmaceuticals, Inc.**
PDUFA Due Date	**2/18/2006**	**Priority Classification**	**3-S**
Division Due Date		**Relevant IND**	**IND 71,161**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
Human PK Summary	X			
Labeling	X			

Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		**RLD: Aleve tablets PRACS Protocol No. R03-725**
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	**X**	**1**		**Comparative dissolution with Aleve Doc No. J4-264A**
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	**X**			**Ask for waiver for pediatric patients age 12 year and below**
Literature References	**X**			
Total Number of Studies		**2**		

Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm ?	X			
QBR questions (key issues to be considered)	• Is the new formulation of naproxen soft gelatin capsule bioequivalent to the reference listing drug, Aleve, under the fasting condition in adults? • What is the food effect of this new dosage form?			
Other comments or information not included above				
Primary reviewer Signature and Date	Lei Zhang, 6/7/2005			
Secondary reviewer Signature and Date	Dennis Bashaw, 6/7/2005			

CC: NDA 21-920, HFD-850 (P. Lee), HFD-560 (Shay), HFD-880 (L. Zhang, Bashaw, Lazor, Selen), CDR

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/s/

Lei Zhang
6/10/05 04:26:03 PM
BIOPHARMACEUTICS

Dennis Bashaw
6/10/05 04:33:55 PM
BIOPHARMACEUTICS