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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.

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