CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-920

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	21-920
Submission Number	N-000
Submission Code	BM
Letter Date	April 15, 2005
Stamp Date	May 11, 2005
PDUFA Goal Date	February 18, 2005
Reviewer Name	Karen B. Feibus, M.D.
Review Completion Date	December 27, 2005
Established Name	Naproxen sodium
(Proposed) Trade Name	not known
Therapeutic Class	nonsteroidal anti-inflammatory
Applicant	Banner Pharmacaps, Inc.
Priority Designation	S
Formulation	Capsules, 220 mg
Dosing Regimen	1-2 capsules, then 1 capsule Q 8 12 hours
Indication	fever reduction, temporary relief of minor aches and pains
Intended Population	Ages 12 years and older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, this application should be approved if prior to the PFUFA data, the sponsor submits labeling with directions for use that inform consumers to take the drug on an empty stomach. This request is based on the results of the relative bioavailability study results in the non-fasting state.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activities are required other than compliance with required periodic reporting.

1.2.2 Required Phase 4 Commitments

If approved, the sponsor will be required to submit pediatric studies in children ages six months to 11 years of age prior to the end of granted deferral period.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical development program for the proposed naproxen product is based on demonstration of the relative bioavailability of the product to the reference listed drug (RLD).

1.3.2 Efficacy

No efficacy data was submitted with this 505(b)(2) application. Efficacy data is referenced from the RLD, Aleve® (NDA 20-204).

1.3.3 Safety

This application primarily relies on safety data referenced in NDA 20-204. Among the 56 subjects who completed the two submitted biopharmacology studies, no new safety signals were detected. No serious adverse events occurred. Only three adverse events occurred following use of the proposed drug product, one of which (headache) was considered probably related to drug study drug treatment.

No new safety signals were evident from the eleven published studies reviewed by the sponsor. The one nested case-control study submitted by the sponsor that addressed cardiovascular or cerebrovascular risk with naproxen use did show some increased risk (adjusted RR = 1.27) with use within three months of the index event; however, data was based on naproxen prescriptions in the United Kingdom and use probably does not reflect nonprescription doses or durations of use.

1.3.4 Dosing Regimen and Administration

Dosing of the proposed drug product will be identical to the RLD, Aleve®.

1.3.5 Drug-Drug Interactions

Naproxen is highly protein bound; therefore, there is a theoretical potential for interaction with other albumin-bound drugs like coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Due to competition at protein binding sites, unbound portions of drug may change and dose adjustments may be needed.

Drug-drug interactions may occur between naproxen and aspirin, angiotensin converting enzyme inhibitors, anticoagulants and thrombolytic agents, diuretics, lithium, methotrexate, and probenecid.

Potential drug-drug interactions are addressed through the class warnings for OTC NSAIDs published June 15, 2005. Some of these warnings contain more specific language than others. These Drug Facts label warnings instruct consumers to:

Ask a doctor before use if you have:

- bleeding problems
- high blood pressure
- heart of kidney disease,
- taken a diuretic
- reached age 60 or older.

Ask a doctor or pharmacist before use if you are:

- Under a doctor's care for any serious condition
- Taking a blood thinning (anticoagulant) or steroid drug

- Taking any other drug.

1.3.6 Special Populations

None

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Naproxen sodium is a FDA-approved nonsteroidal anti-inflammatory (NSAID) and analgesic agent marketed over-the-counter (OTC) in tablet form at a dose of 220 mg. Banner Pharmacaps, Inc. has developed a naproxen sodium 220 mg soft gel capsule and has filed a 505b2 new drug application for this new dosage form. The NDA contains data on two clinical bioequivalence studies comparing the proposed naproxen sodium capsules, 220 mg, to the reference listed drug (RLD), Aleve®. The sponsor proposed use of this product by individuals ages 12 years and older for the following indications:

> 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.

If approved, the proposed naproxen product would need to follow the labeling for the RLD.

2.2 Currently Available Treatment for Indications

Naproxen sodium 220 mg, ibuprofen 200 mg, acetaminophen (APAP) 325 mg and 500 mg, ketoprofen 25 mg, and acetyl salicylic acid (ASA) are currently marketed OTC for the same indications (temporary fever reduction, temporary relief of minor aches and pains).

2.3 Availability of Proposed Active Ingredient in the United States

In 1976, naproxen sodium (275 mg) was approved by FDA as a prescription analgesic. Prescription indications for use include: the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, tendonitis, bursitis, acute gout, and the management of pain and primary dysmenorrhea. In January 1994, FDA granted OTC approval for naproxen sodium 220 mg for:

> 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. Directions state that consumers should not exceed two tablets (440 mg) in any twelve hour period.

Use of naproxen sodium and other NSAIDs is associated with an increased risk of: gastrointestinal adverse effects, severe skin reactions, and renal insufficiency in individuals with underlying renal compromise.

On April 7, 2005, FDA published a public health advisory and announcement outlining requested labeling changes for all COX-2 selective and non-selective prescription NSAIDs and OTC NSAIDs. Long-term controlled clinical trial data with cardiovascular endpoints are not available for most NSAIDs; however, the available data suggest that chronic use of these drugs may increase the risk for cardiovascular and cerebrovascular thromboembolic events. The available data do not suggest an increased risk of these events with short-term, low-dose use of NSAIDs available over the counter.

Based on previously known potential adverse events and more recent concerns about potential thromboembolic adverse events associated with NSAID use, FDA is requiring the following label warnings and information on NSAID Drug Facts labels (published 06/15/2005):

10 APPENDICES

10.1 Line-by-Line Labeling Review

The labeling is reviewed by Michael Koenig, interdisciplinary scientist from the Division of Nonprescription Regulatory Development, in a separate document. His review may be found in DFS.

10.2 Pediatric Study Waiver Request: Consult response from the Division of Over-the-Counter Drug Products

Date: July 12, 2004

From: Karen B. Feibus, M.D.
Medical Officer, Division of Over-the-Counter Drug Products

Through: Andrea Leonard-Segal, M.D.
Medical Team Leader, Division of Over-the-Counter Drug Products

Through: Charles J. Ganley, M.D.
Director, Division of Over-the-Counter Drug Products (HFD-560)

To: Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)

Subject: Request for Pediatric Waiver for Naproxen Sodium Softgel Capsules, 220 mg

Sponsor: Banner Pharmacaps, Inc.

Introduction
This consultation from the Division of Over-the-Counter Drug Products evaluates Banner Pharmacaps' pediatric waiver request for their ANDA application for Naproxen Sodium Softgel Capsules.

Background
On October 19, 2002, Banner Pharmacaps, Inc. filed a citizen petition (CP) with FDA requesting a change of dosage form for Naproxen Sodium, 220 mg from tablet to soft gelatin capsule. The change in dosage form was for submission of an abbreviated new drug application (ANDA) referencing the Reference Listed Drug (RLD), Bayer Corporation's Aleve ® (Naproxen Sodium,

220 mg tablets). In addition, Banner requested a waiver of the requirement to perform pediatric studies, in accordance with 21 CFR 314.55(c)(2), based on the following reasons:

1. The effectiveness of the proposed drug product can be extrapolated from adequate and well-controlled studies in adult and pediatric populations;
2. The dosing and safety data for relevant age groups is well-defined;
3. The innovator product has a 10 year history of use in ages 12 – 17 as an OTC drug product.
4. The drug product is not labeled with dosage recommendations in children less than 12 years old.

HFD-600 reviewed the submission and on February 25, 2002, granted approval of Banner's suitability petition for the change in dosage form under section 505(j)(2)(C)(i) of the Food, Drug, and Cosmetic Act. The change in dosage form was not found to pose questions of safety or effectiveness because the uses, dose, and route of administration of the proposed drug product were the same as the RLD. HFD-600 stated that if the proposed product met bioavailability requirements, then it could be expected to have the same therapeutic effect as the RLD. In the approval letter, FDA informed Banner Pharmacaps that there was no obligation to conduct pediatric studies on the proposed Naproxen Sodium product at that time due to the October 17, 2002, decision by the United States District Court for the District of Columbia, which ruled that the FDA did not have the authority to issue the Pediatric Rule and could not enforce it.

On January 7, 2003, the 108th Congress of the United States of America signed the Pediatric Research Equity Act of 2003 (PREA) into law. Section 505B is titled: Research into Pediatric Uses for Drugs and Biological Products. This amendment to the Food, Drug, and Cosmetic Act requires the following for new drug products:

1. A person who submits an application under section 505 for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration will submit the following assessments:

   - The application will contain appropriately gathered data using appropriate formulations for each age group. The data will be adequate to assess the safety and effectiveness of the drug for the claimed indication with the stated dose and route of administration in all relevant pediatric subpopulations.
   - If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, then FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults with the provision of supplemental information obtained in pediatric subjects, such as pharmacokinetic data.
   - A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.

2. At the request of the applicant, the FDA may defer submission of some or all required pediatric assessments until a specified date after drug approval if:

- the drug is ready for approval for use in adults before pediatric studies are complete or
- if there is another appropriate reason for deferral as determined by FDA.

The applicant's deferral request will include:
- certification of the grounds for deferring the assessments;
- a description of the planned or ongoing studies;
- evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

3. A full or partial waiver of these requirements will be granted at the request of the applicant or on the initiative of the FDA if the applicant certifies and the FDA finds that:

   - necessary studies are impossible or highly impractical
   - there is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups
   - the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients
   - the drug is not likely to be used in a substantial number of pediatric patients
   - reasonable attempts to produce a pediatric formulation necessary for a particular age group have failed.

   If the FDA grants a full or partial waiver due to evidence that a drug product would be ineffective or unsafe in pediatric populations, the information will be reflected in labeling.

With the passage of PREA, HFD-600 suspended approval of Banner's suitability petition for Naproxen Sodium Capsules, 220 mg, and the sponsor was informed that they could submit a request for a waiver of the pediatric study requirement with supporting information and documentation as required by PREA. Approval could be reinstated if a full waiver was granted.

Amendment to Suitability Petition for Naproxen Sodium Capsules, 220 mg
On February 18, 2004, Banner Pharmacaps, Inc. submitted an amendment to the ANDA suitability petition for Naproxen Sodium Capsules, 220 mg, requesting a full waiver of the pediatric study requirements based on the following claims:

1. **Naproxen sodium does not represent a meaningful benefit over existing therapies for pediatric patients.**
   - Acetaminophen, aspirin, and ibuprofen are available in multiple OTC pediatric formulations and labelled for the temporary relief of: fever and minor aches and pains due to the common cold, flu, headache, sore throat, and toothaches. Acetaminophen is also labelled for the temporary relief of aches and pains due to immunizations, sprains, muscle aches, and overexertion. Acetaminophen is labelled for children ages two years

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review is being completed by Rao Puttagunta, chemist from the Office of New Drug Quality Assurance

3.2 Animal Pharmacology/Toxicology

There are no animal pharmacology/toxicology data submitted to this application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The two pharmacokinetic studies submitted with this 505(b)(2) application are the only sources of clinical data.

4.2 Tables of Clinical Studies

Table 2: Clinical studies submitted to NDA 21-920

Study	Subjects
A relative bioavailability study of 220 mg naproxen sodium soft gelatin capsules under fasting conditions	28 enrolled 27 completed
A relative bioavailability study of 220 mg naproxen sodium soft gelatin capsules under non-fasting conditions	30 enrolled 29 completed

4.3 Review Strategy

The safety data from the two relative bioavailability studies was reviewed and the adverse events were evaluated for association with drug treatment and against the well-established safety profile for nonprescription naproxen sodium.

4.4 Data Quality and Integrity

A Division of Scientific Investigation site inspection was requested to evaluate the analytical portion of the bioequivalence study conducted under fasting conditions. This report is currently pending completion.

4.5 Compliance with Good Clinical Practices

The two bioavailability studies were conducted in compliance with good clinical practices.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators and there are no questions raised regarding study integrity.

5 CLINICAL PHARMACOLOGY

The biopharmacology review was completed by Lei Zhang, pharmacologist in the Office of Clinical Pharmacology and Biopharmaceutics. The test product and reference product, Aleve ®, demonstrated dissimilar dissolution profiles with 60% of the test product dissolved at 15 minutes compared to > 95 % of the reference product. At 30 minutes, about 77% of the test product was dissolved versus 100% of the reference product. In both fasting and non-fasting relative bioavailability studies, the test product had a lower C_{max} and longer T_{max} than the RLD. In the fasting state, the differences in C_{max} fell within the equivalence range for relative bioavailability. The T_{max} for Aleve was 0.99 hours compared to 1.42 hours for the proposed product but this difference was felt to be clinically undetectable. Food decreased the rate of absorption (AUC unchanged) for both the proposed naproxen capsules and Aleve®. For Aleve, C_{max} was 15% lower and T_{max} was 1.5 hours longer in the fed state compared to the fasting state, but the effective naproxen serum level of 15,000 ng/mL was achieved within one hour. For the proposed product, C_{max} was 20% lower and T_{max} was 2.3 hours longer in the fed state. Effective serum levels of naproxen were not attained for almost two hours, and this was felt to be a clinically significant difference.

5.1 Pharmacokinetics

Naproxen is rapidly and completely absorbed from the gastrointestinal tract and has in-vivo bioavailability of 95%. Following administration of naproxen sodium tablets, peak plasma levels are attained in 1 – 2 hours. The elimination half-life for naproxen sodium ranges from 12 – 17 hours. Steady-state levels of naproxen are reached in 4 – 5 days of continuous treatment, and the degree of naproxen accumulation is consistent with the drug's half life.[3, 4]

Naproxen is extensively metabolized by the liver to 6-desmethylnaproxen. Approximately 95% of the drug is excreted in the urine in a variety of forms: unchanged drug (< 1%), 6-desmethylnaproxen (< 1%), and different conjugated compounds formed from these two precursors (66 – 92%). The half-lives of naproxen metabolites are less than 12 hours. Less than 5% of the drug is excreted in the feces.

Table 3 presents potential naproxen-associated drug-drug interactions. [3, 4]

Table 3: Naproxen-associated drug-drug interactions	
Drug	**Effect**
Protein bound drugs	Naproxen is highly protein bound; therefore, there is a theoretical potential for interaction with other albumin-bound drugs like coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Due to competition at protein binding sites, unbound portions of drug may change and dose adjustments may be needed.
Aspirin	Concomitant administration of naproxen and aspirin is not recommended. Naproxen is displaced from its protein binding sites by aspirin and this leads to lower plasma concentrations of naproxen and lower peak plasma levels.
ACE inhibitors	Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors and may potentiate renal disease states.
Anti-coagulants and thrombolytic agents	Administration of naproxen with warfarin results in a slight increase in free warfarin in serum but does not affect the hypoprothrombinemic effect of warfarin. Because naproxen may cause GI bleeding and may inhibit platelet aggregation, it should be used with caution inpatients receiving any anticoagulant or thrombolytic agent.
Furosemide/ Thiazides	Clinical studies and postmarketing observations suggest that NSAIDs can reduce the natiuretic effect of furosemide and thiazides in some patients. This effect is attributed to NSAID inhibition of renal prostaglandin synthesis
Lithium	NSAID inhibition of renal prostaglandin synthesis may decrease the renal clearance of lithium by 20% and increase mean lithium serum concentrations by 15%. When NSAIDs and lithium are administered concurrently, close monitoring of lithium levels and observation for lithium toxicity are warranted.
Methotrexate	Concomitant administration of a NSAID with methotrexate may increase serum methotrexate levels and cause toxicity. This effect may be due to NSAID inhibition of renal prostaglandin synthesis.
Probenecid	Administration of probenecid with naproxen substantially increases the plasma half-life of naproxen and plasma naproxen concentrations. Probenecid may interfere with plasma clearance through inhibition of naproxen glucuronidation and renal clearance.

Results of a study in diabetic patients taking tolbutamide showed that administration of naproxen did not effect plasma glucose concentrations.

5.2 Pharmacodynamics

The sodium salt of naproxen is more rapidly absorbed than free naproxen due its increased aqueous solubility. The mechanism of action of the naproxen anion, while not completely understood, is related to prostaglandin synthetase inhibition. [3, 4]

For prescription strengths of naproxen sodium, a reduction in daily dose is recommended for individuals with compromised renal or liver function to help prevent unintentional adverse events and their sequelae including renal failure. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min). Renal toxicity has been seen with naproxen use in individuals with prerenal conditions where renal prostaglandins serve a supportive role in maintaining adequate renal perfusion. The administration of a NSAID to these individuals may cause a dose-dependent reduction in prostaglandin formation and may precipitate renal failure. Individuals at greatest risk include those who: are elderly; have impaired renal function, hypovolemia, heart failure, liver dysfunction, or salt depletion; or use diuretics, ACE inhibitors, or angiotensin receptor blockers. [1]

5.3 Exposure-Response Relationships

Not applicable.

6 INTEGRATED REVIEW OF EFFICACY

No efficacy data were submitted with this 505(b)(2) application.

7 INTEGRATED REVIEW OF SAFETY

The sponsor submitted two relative bioavailability studies conducted in a total of 59 subjects. This portion of the review will present the adverse event data from these studies. The sponsor has not submitted a safety update with the application.

7.1 Methods and Findings

The sponsor submitted results from two relative bioavailability studies, one fasting and one non-fasting. The protocols were identical except for the subjects' feeding condition. The protocol for the fasting study is described below. Afterwards, protocol differences in the non-fasting study are described.

Objectives

A Phase III clinical study to evaluate the bioequivalence of Banner Pharmacaps Inc. naproxen sodium 220 mg soft gelatin capsules to the reference listed drug (RLD), Bayer's Aleve® 220 mg tablet (NDA 20-204)

Study Design

Randomized, single-dose, two-way crossover study under fasting conditions
Minimum washout period between doses is 14 days.

Informed Consent
Informed consent was obtained prior to the screening process. The consent form was submitted with the protocol.

Population

- 26 or 30 healthy volunteers age 18 years or older.
- Recruitment will be from the community at large including university students.
- Inclusion Criteria:
  1. healthy men and women, 18 years or older
  2. weight will not exceed ±20% for height and body frame according to the Desirable Weight for Adults table (1983 Metropolitan Height and Weight Table)
  3. screening completed within 28 days of dosing
  4. females of childbearing potential or who are not postmenopausal for one year will use an acceptable method of birth control for the duration of the study (condom with spermicide, diaphragm with spermicide, intrauterine device, abstinence)

- Exclusion Criteria:
  1. recent history of drug or alcohol addiction or abuse
  2. presence of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease as determined by the investigator
  3. clinical laboratory test values outside the accepted reference range and on repeat testing are deemed clinically significant
  4. reactive hepatitis B surface antigen screen
  5. reactive HIV
  6. positive drug abuse screen
  7. positive pregnancy test
  8. breastfeeding
  9. history of allergy to naproxen sodium or related drugs
  10. history of clinically significant allergies, including drug allergies
  11. clinically significant illness during the four weeks prior to Period I dosing
  12. use of tobacco products
  13. use of any drug known to induce or inhibit hepatic drug metabolism during the 28 days prior to Period I dosing
  14. blood donation of more than 150 ml in the 28 days prior to Period I dosing
  15. plasma donation within 14 days prior to Period I dosing
  16. taken any investigational drug within 28 days of Period I dosing
  17. use of any systemic prescription medication within 14 days of Period I dosing

Treatment Plan (Medication, Administration, Duration, Timing, Visits, etc)

- Screening was completed within 28 days of first study medication dosing.

- Study check-in: brief evaluation of each subject to confirm that inclusion and exclusion criteria were still met. Serum pregnancy test drawn on female subjects.

- Subjects were confined at the study center for 10 hours prior to dosing and at least 24 hours after dosing for each of the two study periods.

- Subjects were randomized to receive either the test product or the RLD at the first study dose. All subjects received the other study medication at the second study dose. There was a minimum of 14 days between study medication doses.

  Test product: 2 x 220 mg naproxen sodium capsules
  RLD: 2 x 220 mg Aleve® 220 mg naproxen sodium tablets

- A light snack was given 10 hours before dosing. Subjects drank water ad lib until one hour prior to dosing and was offered 240 mL of water two hours after dosing. Unlimited oral intake resumed four hours after the study medication was taken. Subjects were required to remain upright for four hours after dosing.

Data Collection

- During screening, subjects underwent a medical history, physical exam, ECG, and blood draw for CBC, chemistries, HIV, and pregnancy (females only). A urine sample was collected for urinalysis and urine drug screen.

- During each of the two study periods, blood was drawn from the study subjects prior to dosing and then:
  - every 20 minutes for the first 2 hours after dosing
  - every 30 minutes for the third hour after dosing
  - at hours 4, 6, 8, 12, 16, 24, 36, 48, and 72 after dosing.

- Study exit procedures were completed within 14 days of the last study blood draw. A physical exam was performed and blood was drawn for CBC, serum chemistries, and pregnancy testing (females only).

The protocol for the non-fasting relative bioavailability study differed from the fasting study, described above, in the following ways:

- Following an overnight fast, subjects were served a standardized, high fat breakfast 30 minutes prior to study drug administration. The breakfast consisted of the following:
  - 2 eggs fried in butter
  - 4 oz. hash brown potatoes
  - 2 strips of bacon
  - 2 slices of toast with butter
  - 8 fluid ounces (240 mL) whole milk
- After eating breakfast, subjects were sequentially dosed at one minute intervals. The actual time of dosing was recorded on the Master Flow Sheet. Under direct observation, medication was taken with 240 mL of room temperature water.

- Except for the water given with the study drug and the milk with breakfast, no fluid was allowed from one hour prior to dosing until one hour after dosing.
- Two hours after dosing, all subjects consumed 240 mL of water.
- Subjects fasted for 4.25 hours after study drug administration. Subjects were served standardized meals and beverages. No grapefruit products, caffeine, or xanthine-containing food or drink were allowed during the confinement portion of the study.

7.1.1 Deaths

No deaths occurred in the relative bioavailability studies. The sponsor did not submit a safety update, so further data is not available.

7.1.2 Other Serious Adverse Events

There were no serious adverse events in either relative bioavailability study.

7.1.3 Dropouts and Other Significant Adverse Events

Subject 14 in the fasting bioavailability study was discontinued from the study due to a positive pregnancy test at the Period II check-in. The positive pregnancy was recorded as an adverse event and the subject was to be monitored for the duration of her pregnancy. The sponsor did not report an outcome for the pregnancy and did offer information about her estimated date of delivery.

In the non-fasting bioavailability study, Subject 12 discontinued from the study prior to the Period II check-in due to a family emergency.

7.1.3.1 Overall profile of dropouts

The two drop-outs from the clinical biopharmacology studies are described above. No subjects discontinued the studies due to adverse events.

7.1.3.2 Adverse events associated with dropouts

The two drop-outs from the clinical biopharmacology studies are described above. No subjects discontinued the studies due to adverse events.

7.1.3.3 Other significant adverse events

There were no other significant adverse events.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events submitted with this application are presented below.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Given that there were only 16 adverse events (AEs) among 12 subjects in the two relative bioavailability studies, the sponsor did not classify the adverse events by body system. MedDRA terminology was used, with clarification when needed.

7.1.5.3 Incidence of common adverse events

Among the 56 subjects who completed the two bioavailability studies, 12 (21.4%) experienced one or more non-serious adverse events. In the investigator's opinion, only one AE (headache) during the fasting study and none of the AEs in the non-fasting study were probably related to study drug. Fourteen AEs were classified as unrelated to study drug, and one (epistaxis) was classified as remotely related to study drug. Three subjects experienced four of the 16 adverse events after taking the proposed naproxen capsule test product. Nine subjects experienced 12 of the 16 adverse events after taking the RLD, Aleve®. Table 4 below summarizes the adverse events experienced by study subjects by study, by drug, and by relationship to drug.

7.1.5.4 Common adverse event tables

Table 4: Adverse events by study, subject, study drug, and relationship to study drug			
Study/Subject F = fasting NF = non-fasting	**Study Drug**	**Event (incidence)**	**Relationship to study drug**
F-01	RLD	Shooting pain, venipuncture site (1.8%)	unrelated
	RLD	Burning, venipuncture site (1.8%)	unrelated
F-02	Test	Lower back pain (1.8%)	unrelated
F-08	RLD	Oral pain (left side of mouth) (1.8%)	unrelated
F-13	RLD	Headache (3.6%)	probable
F-14	RLD	Pregnancy (1.8%)	unrelated
F-15	Test	Post-nasal drip (1.8%)	unrelated
	Test	Epistaxis (1.8%)	remote
F-21	RLD	Vomiting (1.8%)	unrelated
NF-02	RLD	Nasopharyngitis (head cold) (1.8%)	unrelated
NF-03	Test	Headache (3.6%)	unrelated
NF-08	RLD	Pallor (1.8%)	unrelated
	RLD	Hyperhidrosis (1.8%)	unrelated
NF-17	RLD	Dizziness (light-headed) (1.8%)	unrelated
	RLD	Nausea (1.8%)	unrelated
NF-22	RLD	Hematoma, venipuncture site (1.8%)	unrelated

7.1.5.5 Identifying common and drug-related adverse events

One subject experienced a headache after taking Aleve® that was considered probably related to study drug. An episode of vomiting after taking naproxen sodium on an empty stomach was classified as unrelated to study drug.

Reviewer comment:

1. *Given that naproxen sodium carries an indication for the treatment of headache and that this study subject was fasting, it is not clear how the investigator concluded that this AE was probably related to study drug. It would be helpful to understand how the investigator determined that an episode of headache was deemed probably related to study drug, whereas an episode of vomiting was classified as not related to study drug when NSAIDs are not well-tolerated by some individuals, especially on an empty stomach.*

2. *The adverse events that occurred in the bioavailability studies for naproxen sodium soft gelatin capsules raise no new safety concerns.*

7.1.5.6 Additional analyses and explorations

None.

7.1.6 Less Common Adverse Events

All adverse events are presented under common adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Blood and urine samples were collected at the screening visits for both studies. Hematology, clinical chemistries, urinalysis, serology, pregnancy test (in females), and urine drug screen evaluations were done. All results were reviewed by the clinical investigators prior to the Period I dose. At the study exit visit, blood samples were collected for hematology, clinical chemistries, and pregnancy test (in females), and all results were reviewed by the investigators. Values outside the normal range were either classified as *not clinically significant* or follow-up testing was requested.

Hepatitis B surface antigen, HIV, and urine drug screens were non-reactive for all 58 subjects enrolled in the two studies.

While there were no clinically significant changes in clinical laboratory measurements during either study that could be reasonably associated with the administered study drugs, six subjects had abnormal laboratory values that were considered clinically important and were followed. This information is displayed in Table 5.

Table 5: Subjects with abnormal laboratory values and results of follow-up testing

Study/subject F = fasting NF = non-fasting	**Laboratory parameter**	**Result**	**First repeat result**	**Second repeat result**	**Disposition/ comment**
F-03	Hgb/Hct MCV/MCH	10.0/30.7 71.5/23.3	9.4/29.8 -	9.5/30.1 -	Follow-up (F/U) continues
F-08	WBC neutrophils	2.6 1.3	3.9 1.9	-	Considered not clinically significant. No further F/U
F-09	Total bilirubin	3.0	3.1	1.8	Elevation mild, considered not clinically significant. No further F/U.
F-13	Blood glucose	144	94		Second reading normal
NF-23	ALT (SGPT)	55	53	38	Spontaneous return to normal
N-28	Blood glucose	127	90		Second reading normal

Reviewer comment:

1. *In this reviewer's opinion, the anemia in subject F-03 and the elevated total bilirubin in subject F-08 should be evaluated by a healthcare provider; however, none of these laboratory abnormalities appear to be related to the use of study drug.*

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Naproxen sodium has a well-established adverse event/safety profile. The sponsor is referencing the safety data from NDA 20-204. Laboratory abnormalities among study subjects are summarized below. No laboratory abnormalities related to drug treatment were identified.

7.1.7.3 Standard analyses and explorations of laboratory data

No statistical analyses were performed on the laboratory data collected on the 56 biopharmacology study subjects. Laboratory abnormalities were discussed above.

7.1.7.4 Additional analyses and explorations

None.

7.1.7.5 Special assessments

None.

7.1.8 Vital Signs

Blood pressure and heart rate were measured prior to dosing, at 12 and 24 hours after dosing, and upon completion of the study. All measurements were normal except for the following measurements, which were repeated. Table 6 lists abnormal vital sign results and follow-up values.

Table 6: Abnormal vital sign assessments and follow-up results

Study subject F = fasting NF = non-fasting	**Study period/ Study hour**	**Initial BP, HR**	**Repeat assessment**
F-15	Period I/ -1.0	114/71, 108	HR = 107
	Period II/ 72.0	115/80, 104	HR = 100
F-17	Period I/ -1.0	86/52, 62	Systolic BP = 90
	Period II/ 12.0	84/53, 68	BP = 92/53, HR = 75
NF-06	Period II/ 12.0	84/47, 84	BP = 91/50, HR = 75
NF-08	Period I/ -1.0	105/68, 104	HR = 96
	Period II/ 72.0	122/75, 102	HR = 104
NF-09	Period II/ 12.0	115/74, 121	BP = 107/67, HR = 93

Reviewer comments:

1. *Appropriate follow-up measurements were performed for abnormal blood pressure and heart rate values. None of these vital sign assessments are clinically concerning.*

2. *This reviewer notes that the subjects who required repeat vital sign assessments were not the subjects who had abnormal laboratory results.*

7.1.8.1 Overview of vital signs testing in the development program

All information on vital sign assessment in the two biopharmacology studies is provided above.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were performed on all eligible subjects at enrollment but were not repeated during the study. QT interval studies were not conducted for this 505(b)(2) application. At enrollment, all subjects met inclusion and exclusion criteria and this included an *acceptable* ECG. The investigators do not define ECG readings other than normal sinus rhythm that would be *acceptable*.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Not applicable

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

No preclinical studies are required for this 505(b)(2) application.

7.1.11 Human Carcinogenicity

No preclinical studies are required for this 505(b)(2) application.

7.1.12 Special Safety Studies

No special safety studies were conducted for or submitted with this 505(b)(2) application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Naproxen sodium is not associated with any known withdrawal phenomena or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

The sponsor did not provide any data on naproxen and pregnancy, so the following data represents this reviewer's review of the subject.

Maternal use of naproxen and other NSAIDs during the third trimester of pregnancy may be associated with neonatal renal failure, oligohydramnios, premature closure of the ductus arteriosus, and consequent problems in perinatal adaptation including pulmonary hypertension.[5] For these reasons, OTC ibuprofen products carry the following warning on the label:

> **If pregnant or breast-feeding**, ask a health professional before use. It is especially important not to use naproxen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Prescription labeling for naproxen contains the following information regarding use in pregnancy and breastfeeding:[1]

> #### Pregnancy
>
> In late pregnancy, as with other NSAIDs, naproxen should be avoided because it may cause premature closure of the ductus arteriosus.
>
> #### Teratogenic Effects
>
> *Pregnancy Category C*
>
> Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m ^{2} /day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m ^{2} /day, 0.27 times the human systemic exposure),

and mice at 170 mg/kg/day (510 mg/m ^{2} /day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naproxen should not be used during pregnancy unless clearly needed.

Nonteratogenic Effects

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during third trimester should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

Nursing Mothers

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Spontaneous Abortion:
Since 2001, data from a cohort study and a case-control study suggest that there may be an increased risk of spontaneous abortion associated with the use of NSAIDs during conception and the first trimester of pregnancy. There are many confounding factors that influence the interpretation of data from these studies.

- A case-control study by Nielsen et al (2001) suggested that women who received a prescription for any NSAID had an increased risk of miscarriage within 12 weeks following receipt of the NSAID prescription. The authors found an odds ratio for miscarriage as high as 6.99 when the prescription was filled within one week of miscarriage and as low as 2.69 when the prescription was filled 7 – 9 weeks prior to miscarriage. Results are confounded by: unknown patient compliance with medication, unknown reasons for which the NSAID was prescribed, gestational age at the time of miscarriage, lack of data regarding OTC NSAID use, and cases and controls that were not well-matched for gestational age. In 2004, Nielsen et al updated their dataset to include pregnant women from 1998- 2002, and gestational age information was available. A numerically positive correlation was found between miscarriage and exposure to a NSAID during the first 9 weeks of gestation (adjusted odds ratios were 1.59 – 3.35), but none of these numbers were statistically significant (all confidence intervals crossed 1.0).[6, 7]

- In 2002, Li et al published a prospective cohort study that evaluated risk factors for miscarriage among pregnant members of a regional HMO program. Women were enrolled prospectively upon diagnosis of pregnancy but information on the use of NSAIDs and other medications was collected retrospectively. Information was collected on the name of the medication and its duration and frequency of use; however, there was no information on dosing. Seventy-five (5%) of 1055 women reported NSAID use. Any NSAID use was associated with an adjusted hazard ratio of 1.8 (CI = 1.0 – 3.2). NSAID use at conception was associated with an adjusted hazard ratio of 5.6 (CI = 2.3 – 13.7). NSAID use longer than one week was associated with an adjusted hazard ratio of 8.1 (CI = 2.8 – 23.4). There were only six women who used NSAIDs at the time of conception and five women who used the product for more than one week. These results are confounded by retrospective data collection on medication use, use of a cohort initially recruited and interviewed for a different purpose, lack of information regarding medication doses, and a small population of NSAID users in the study.[2]

7.1.15 Assessment of Effect on Growth

Pediatric subjects have not been assessed. Growth studies were not conducted.

7.1.16 Overdose Experience

The PDR entry for naproxen sodium provides the following information regarding overdose:

> Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters, and greater than 1000 mg/kg in dogs.
>
> Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

7.1.17 Postmarketing Experience

The safety update was not submitted by the sponsor. Adverse event reporting through the AERS database has not revealed a new safety signal with the use of naproxen and naproxen sodium at nonprescription doses. Based on findings of increased cardiovascular risk with the chronic, long-term use of rofecoxib, class warnings for cardiovascular risk have been placed on all OTC NSAID products; however, to date, no increased risk has been identified with short-term NSAID use at nonprescription doses.

7.2 Adequacy of Patient Exposure and Safety Assessments

This is a 505(b)(2) application relying on pre-clinical and clinical safety data from NDA 20-204 and the post-marketing information available for this product. The only clinical data submitted were from the two biopharmacology studies for establishing relative bioavailability. A safety update was not included in the submission and has been requested from the sponsor.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

No new adverse event signals were detected in the biopharmacology safety data.

7.4 General Methodology

There are no issues for discussion in this section. Clinical data was provided from two biopharmacology studies that enrolled a total of 58 subjects.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

No applicable.

7.4.1.1 Pooled data vs. individual study data

Not applicable.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

Not applicable.

7.4.2.1 Explorations for dose dependency for adverse findings

Nonprescription dosing for naproxen sodium is well established.

7.4.2.2 Explorations for time dependency for adverse findings

The adverse event profile for nonprescription naproxen sodium is well established. Nonprescription use is limited to 10 days duration through labeling.

7.4.2.3 Explorations for drug-demographic interactions

Drug-drug interactions associated with naproxen are discussed in section 5.1 of this review.

7.4.2.4 Explorations for drug-disease interactions

Issues regarding the interaction of naproxen with impaired renal function and prerenal conditions are presented in section 5.2 of this review.

7.4.2.5 Explorations for drug-drug interactions

No new exploration for drug-drug interactions was done for this submission.

7.4.3 Causality Determination

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen and administration of the proposed drug product will be identical to the reference listed drug, Aleve®.

8.2 Drug-Drug Interactions

Please refer to section 5.1 of this review. Adjustment of dosing may be needed in individuals who have compromised renal function, compromised liver function, or are elderly or prerenal. Nonprescription naproxen label warnings address these issues by informing consumers who fall into these groups, to consult their physician prior to using the product. Please see section 2.3 of this review for a full display of the new FDA template for nonprescription NSAID label warnings.

8.3 Special Populations

Not applicable.

8.4 Pediatrics

The sponsor submitted a request for pediatric waiver based on the argument that other NSAIDs are available for the treatment of children under age 12 years and that naproxen sodium would not offer a significant clinical benefit to this age group.

This reviewer and the Division of Nonprescription Clinical Evaluation disagree with the sponsor and believe that there would be substantial clinical benefit in having a pediatric naproxen formulation and dosing instructions for children between the ages of six months and 11 years. The use of aspirin is not recommended in children due to the risk of Reye's Syndrome. Acetaminophen and ibuprofen are the only other drugs available for the treatment of pain and fever in this age group, and the dosing interval is every four to six hours. A medication to treat pain and fever in children that can be dosed every 12 hours could offer benefit in numerous clinical situations. In addition, individual response to a particular NSAID is variable, so having a third drug that to safely and effectively treat fever and pain in children would be clinically valuable.

Please see Appendix A for the Division of Over-the-Counter Drugs consult on this issue. Please see Appendix B for the pediatric consult on this issue.

The sponsor should be given a deferral of specified duration for pediatric studies in children ages six months to 11 years of age. A partial waiver of pediatric studies for children younger than six months of age should be granted.

8.5 Advisory Committee Meeting

There is no advisory committee meeting for this application.

8.6 Literature Review

As a safety update, the sponsor submitted information extracted from eleven published references reporting on 35,000 study subjects. The most commonly observed adverse events for naproxen sodium occurred in the gastrointestinal system (dyspepsia, nausea, and vomiting) and nervous system (somnolence and headache). The gastrointestinal system adverse events tended to occur more frequently with increasing subject age and duration of drug use.

Hippisley-Cox and Coupland (2005) reported a nested case-control analysis that evaluated the risk of myocardial infarction among patients taking COX-2 inhibitors versus conventional non-steroidal anti-inflammatory drugs. This was the only study submitted that reported or specifically evaluated cardiovascular or cerebrovascular adverse events associated with naproxen use. Subjects were 9218 cases with a first ever diagnosis of myocardial infarction during the four year study period. The authors identified 86,349 control cases matched for age, calendar year, sex, and practice, so each case had 10 controls. The study obtained subjects and data from three hundred sixty-seven general practices in the United Kingdom that contribute to the QRESEARCH database. Information on NSAID use was derived from prescription records and

was divided into categories based on whether the drug was used within three months of the cardiac event, more than three months before the cardiac event, or no use of the agent in the past three years.

The relative risk ratio (RR) for myocardial infarction was set to 1.0 for individuals who had not used the particular NSAID in the past three years. For naproxen the adjusted RR for myocardial infarction was 1.09 (0.96 – 1.24) for individuals who had not used naproxen during the three months before the cardiac event, which was not statistically different from 1.0. However, the adjusted RR for myocardial infarction was 1.27 (1.01 – 1.60) for individuals who had used naproxen during the three months prior to the event. This difference was statistically significant. For comparison, the adjusted RRs for ibuprofen with and without use during the three months before myocardial infarction were 1.24 (1.11 – 1.39) and 1.05 (0.98 – 1.12) respectively. For diclofenac, the adjusted RRs with and without use during the three months before myocardial infarction were 1.55 (1.39 – 1.72) and 1.13 (1.05 – 1.21) respectively. No information was provided on naproxen dose or frequency of dosing, but all information was obtained from prescriptions

No new safety signals were evident from the submitted published literature. The new FDA template for NSAID warnings (see pages 6 – 7) includes warnings regarding the possible increased risk of cardiovascular and/or cerebrovascular events if naproxen OTC is used for longer durations than labeled. Appendix 10.4 contains the tabular information and references submitted by the sponsor from their literature review.

This reviewer conducted a literature search and was unable to find any studies addressing cardiovascular risk in individuals using naproxen sodium at non-prescription doses. Other prospective and retrospective studies assessing prescription use of naproxen and the risk of cardiovascular events did not compare the naproxen treatment group to a placebo group or a retrospective comparison group not using a NSAID.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The approvability of this application is primarily based on the relative bioavailability of the proposed drug product to the RLD. According to the biopharmacology reviewer, the proposed naproxen sodium softgel gelatin capsules demonstrated relative bioavailability to the RLD in the

fasting state. Due to significant delay in T_{max}, the proposed product did not demonstrate relative bioavailability to the RLD in the non-fasting state.

No new safety signals were evident from the clinical safety data submitted with the biopharmacology studies or the eleven published studies reviewed by the sponsor. The one nested case-control study submitted by the sponsor that addressed cardiovascular or cerebrovascular risk with naproxen use did show some increased risk (adjusted RR = 1.27) with use within three months of the index event; however, data was based on naproxen prescriptions in the United Kingdom and use probably does not reflect nonprescription doses or durations of use.

9.2 Recommendation on Regulatory Action

In the opinion of this reviewer, this application should be approved if prior to the PFUFA data, the sponsor submits labeling with directions for use [redacted] This request is based on the results of the relative bioavailability study results in the non-fasting state.

9.3 Recommendation on Postmarketing Actions

If the product is approved, the sponsor will need to conduct pediatric studies in children ages six months to 11 years of age.

9.3.1 Risk Management Activity

If the product is approved, the sponsor should submit periodic and annual reports as required for approved NDA drug products. No other risk management activities are requested at this time.

9.3.2 Required Phase 4 Commitments

If the product is approved, the sponsor should receive a deferral of defined duration for pediatric studies in children ages six months to 11 years of age. A partial waiver of pediatric studies for children younger than six months of age should be granted.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The labeling is reviewed by Michael Koenig, interdisciplinary scientist from the Division of Nonprescription Regulatory Development, in a separate document. His review may be found in DFS.

9.5 Comments to Applicant

None.

and older. Ibuprofen is consumer labelled for children six months old and older. Aspirin is labelled for children at least three years old.

- Naproxen sodium, 220 mg, is labelled for OTC use in consumers at least 12 years old for the following indications:

  Temporarily relieves minor aches and pains due to: the common cold, headache, toothache, muscular aches, backache, menstrual cramps, and the minor pain of arthritis. Temporarily reduces fever.

  Most of these indications are shared by the pediatric formulations for acetaminophen, ibuprofen, and aspirin. Arthritis in children is rare and severe and is physician managed with prescription medications.

2. **Naproxen sodium is not likely to be used in a substantial number of pediatric patients.**

   - The average age of menarche in the United States is twelve years. Girls who start menstruating and experience menstrual cramps before the age of 12 do not comprise a substantial number of patients. Girls younger than 12 years of age who experience menstrual cramps should consult their physicians regarding treatment with naproxen sodium 220 mg.

Discussion

Availability of pediatric OTC formulations of naproxen sodium could offer significant benefit over existing therapies to pediatric patients in the temporary relief of fever, minor aches and pains, and menstrual cramps. There is a paucity of published research evaluating the safety and efficacy of naproxen sodium in children under the age of twelve years. A literature search on PubMed using the terms "naproxen, children, pediatric" reveals that most research on the use of naproxen sodium in younger children evaluates its use in the treatment of inflammtory rheumatologic conditions. Most of the literature that evaluates naproxen sodium in the treatment of dysmenorrhea evaluates women ages 16 and above. (Search terms: naproxen, menstrual cramps, dysmenorrhea, children, fever, analgesia)

Currently, naproxen sodium is approved in the United States for the following prescription and OTC indications:

Rx Indications:

- Adults (12 years and older):
  anti-inflammatory uses: 275 – 550 mg po bid
  mild to moderate pain: 550 mg po bid
  ankylosing spondylitis: 550 mg po bid
  dysmenorrhea: 550 mg po bid

acute gout: 275 mg po q 8hrs

- Children:
  juvenile rheumatoid arthritis (JRA): 5 – 10 mg/kg po bid

OTC Indications:

- Adults (12 years and older): 400 mg x 1, then 200 mg po q 8 – 12 hrs
  for the temporary relief of fever and minor aches and pains due to: the common cold, headache, toothache, muscular aches, backache, menstrual cramps, and the minor pain of arthritis.

The potential benefits of OTC naproxen sodium for the pediatric population are as follows:

1. **Longer dosing interval of 8 – 12 hours**
   An eight to twelve hour dosing interval offers a clinically significant benefit over existing therapies for the following reasons:
   - Some children are uncooperative with taking necessary medications. Less frequent dosing makes medicating a child less unpleasant for both the child and the parents.
   - A child being treated around-the-clock for fever or minor aches and pains does not need to be awakened in the middle of the night for more medication.
   - A child who needs treatment with an analgesic for menstrual cramps or minor aches and pains while attending school can take naproxen sodium before leaving for school. The child will not require further medication until the school day has ended. This can be a significant issue as many schools prohibit self-medication and require that all medications be dispensed by the school nurse.
   - Menstrual cramps are a leading cause of recurrent school absenteeism and class absenteeism.[3, 4, 6, 7, 9] An effective treatment dosed two to three times per day could potentially decrease school days missed by young girls who have just started menstruating.

2. **Fever in children: a third medication option**
   The American Academy of Pediatrics (AAP) recommends treating fevers of 101°F or higher when a child exhibits changes in activity level or appears uncomfortable. The AAP recommends treating all fevers of 103°F or more.[5] Articles in the literature support the effectiveness of naproxen sodium for treating fever in children.[1,8] While acetaminophen, ibuprofen, and aspirin all have OTC pediatric formulations and carry a fever indication, only acetaminophen and ibuprofen are recommended by the American Academy of Pediatrics for the treatment of fever in children:

   since aspirin may cause or be associated with side effects such as stomach upset, intestinal bleeding, and (most seriously) Reye syndrome, we do not recommend using it to treat a simple fever.[5]

   All aspirin products carry the following FDA-required warning:
   WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye Syndrome, a rare but serious illness.

3. **Treatment of menstrual cramps (dysmenorrhea) in girls with early menarche**
   Based on data from the Third National Health and Nutrition Examination Survey (NHANES III), the mean age at menarche in the United States is 12.43 years. However, 25% of non-Hispanic whites girls and nearly 50% of non-Hispanic black and Mexican American girls are menstruating prior to their 12th birthdays.[2] Research data suggest that about 65% of these girls will experience menstrual cramps with their *earliest periods*.[9] In a recent study conducted in Croatia, the mean age at menarche was 12.2 – 12.3 years, and 44% of the menstruating 11 year olds in the study had dysmenorrhea. Eleven year olds comprised 3% of the study population of 297 girls.[6]

   Naproxen sodium OTC should be an available dysmenorrhea treatment for girls under the age of 12. Given that the same physiological process causes dysmenorrhea in girls younger and older than 12 years of age, extrapolation between age groups for this indication may be appropriate. Pharmacokinetic studies on naproxen sodium, 220 mg, may be needed at age-appropriate body weights to determine whether a lower dosage should be used for girls of lighter weight and to determine what the lower weight limit for the adult dosage should be.

4. **No indication for arthritis**
   A pediatric formulation of OTC naproxen sodium should not carry an arthritis indication as juvenile rheumatoid arthritis is a serious medical condition that requires active physician diagnosis and management.

Conclusions and Recommendations

1. An OTC pediatric formulation of naproxen sodium could offer significant benefits to the pediatric population in the temporary relief of fever and minor aches and pains due to the common cold, flu, headache, sorethroat, menstrual cramps, muscle aches, sprains, and immunizations.

2. Naproxen sodium should be evaluated for safety and efficacy in the treatment of these conditions in children between the ages of six months and twelve years.

3. The sponsor's request for a full waiver of the pediatric study requirement should be denied. A partial waiver could be granted for children younger than six months of age.

4. If the product is ready for approval for use in adults and children 12 years of age and older, then a deferral would be acceptable.

References:

1. Cashman TM, Starns RJ, Johnson J, Oren J. Comparative effects of naproxen and aspirin on fever in children. J Pediatrics 1979 Oct; 95 (4): 626 – 9.

2. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA et al. Age at Menarche and Racial Comparisons in US Girls. Pediatrics 2003 Jan; 111(1): 110 – 113.
3. Klein JR, Litt IF. Epidemiology of Adolescent Dysmenorrhea. Pediatrics 1981 Nov; 68 (5): 661 – 4.
4. Schroeder B, Sanfilippo JS. Dysmenorrhea and Pelvic Pain in Adolescents. Pediatr Clin North Am. 1999 Jun; 46 (3): 555 – 71.
5. Shelov SP, Hannemann RE. Caring For Your Baby and Young Child, Birth to Age 5. The American Academy of Pediatrics. Bantam Books 1998. 502, 599 – 604.
6. Strinic T, Bukovic D, Pavelic L, Fajdic J, Herman I et al. Anthropological and Clinical Characteristics in Adolescent Women with Dysmenorrhea. Coll Antropol. 2003 Dec 27; 27 (2): 707 – 11.
7. Svanberg L, Ulmsten U. The Incidence of Primary Dysmenorrhea in Teenagers. Arch Gynecol 1981; 230: 173 – 177.
8. Szorady I, Martonyi E, Santa A. Antipyretic Effect of Naprosyn Syrup in Childhood. Therapia Hungarica (English Edition) 1985; 33 (4): 201 – 6.
9. Widholm O. Dysmenorrhea During Adolescence. Acta Obstet Gynecol Scand Suppl 1979; 87: 61 – 66.

10.3 Pediatric Study Waiver Request: Consult response from the Division of Pediatrics

M E M O R A N D U M

Date: November 30, 2005

From: Lisa Mathis, M.D.
Acting Director, Division of Pediatric Drug Development
Office of Counter-Terrorism and Pediatric Drug Development

To: Andrea Leonard Segal, M.D.
OND/ONP/DNCE

Re: Naproxen Sodium pediatric studies

Naproxen sodium, 220 mg is an over-the counter drug, approved for marketing by the FDA for various companies including Roche (Aleve®, NDA 20-204) and Perrigo (ANDA 74-661). They state that naproxen sodium "Temporarily relieves minor aches and pains due to headache, muscular aches, backache, toothache, common cold, menstrual cramps and minor pain due to arthritis. Temporarily reduces fever." It is approved for use in children 12 years old and older for these indications. Naproxen sodium is approved for treatment of pediatric patients with Juvenile Rheumatoid Arthritis (JRA) down to 2 years of age.

Other similar products available over-the-counter are acetaminophen, labeled for children 2 years old and older, aspirin, labeled for children 3 years old and older, and ibuprofen, labeled for children 6 months old and older. Aspirin use in children is discouraged because of the risk of Reyes Syndrome. There are patients who are allergic to ibuprofen. This may leave a pediatric patient with only one OTC medication to treat pain and fever.

Naproxen does appear in handbooks frequently used for dosing medications in pediatrics (Harriet Lane Handbook). The dose referenced for the treatment of pain/fever is 5-7 mg/kg Q8-12 hours. The approved dose for JRA is 10-20 mg/kg Q12 hours.

Recommendation:

Given the potential need for alternatives by some patients, and the lack of dosing information in labeling for over-the-counter indications (other than JRA), it would be beneficial to have pediatric study information for this drug.

OTC antipyretics do not having labeling under 6 months based on safety, and it is recommended that a partial waiver be granted for patients under 6 months.

10.4 Tabular Data and References from Sponsor's Literature Review

TABULAR SUMMARY OF SAFETY DATA ON NAPROXEN SODIUM

Article Citation	Study Type/ Design	Size of Study Population	Adverse Events	Age	Sex	Dose	Duration	Relevant Medical History	Comments
Journal of the American Pharmaceutical Association. 2001; Vol. 41:127-138.	Meta-analysis of 46 studies	4623	*Digestive System* Dyspepsia Nausea Vomiting *Nervous System* Dizziness Headache Somnolence	20-30's low 60's	M/F	220-880mg Of the 46 studies: 22 single dose, 15 multiple dose and 9 PRN	Up to 10 days	Dental pain Sore muscles Arthritis Dysmenorrhea Ankle sprains Colds Endoscopy Fever /Headache Myalgia	Meta-analysis confirmed favorable safety profile for naproxen sodium at OTC levels when adhering to labeled directions. Of the AE's, somnolence, headache and vomiting were significant when compared to placebo.
Clinical Therapeutics. 1995; Vol.17, No. 4: 587-601.	A Randomized, double-blind, placebo controlled clinical trials	8404	*Digestive System* Diarrhea Dyspepsia Nausea Vomiting Constipation *Nervous System* Dizziness Somnolence *Others:* Allergic reactions Asthma Chills Edema Headache Rash	14-86 Avg. 29.4	M/F	187.5-440mg	1-10days	Dental pain Dysmenorrhea Arthritis pain Headache Cold/Sore throat Fever Endoscopy Musculoskeletal pain	Results from the clinical studies suggest naproxen sodium is relatively well tolerated for approved OTC indications and has a side-effect profile similar to that of acetaminophen, ibuprofen, and placebo.

Banner Pharmacaps, Inc. Page 1 of 4 NDA 21-920

Appears This Way
On Original

TABULAR SUMMARY OF SAFETY DATA ON NAPROXEN SODIUM

Article Citation	Study Type/ Design	Size of Study Population	Adverse Events	Age	Sex	Dose	Duration	Relevant Medical History	Comments
BioMed Central Women's Health. 2004; 4:5.	Meta-analysis	231 total 186 NAP	Nausea Somnolence	Avg. 31	F	550mg q12hrs	2 days	Dysmenorrhea	Adverse effects were uncommon suggesting safety in short-term use of naproxen sodium
Clinical Therapeutics. 1997; Vol. 19, No. 4:642-655.	A multicenter, randomized, parallel-group, placebo controlled, double-masked study clinical trial	279 total 92 NAP	*Body as a whole* Abdominal pain Headache *Digestive System* Constipation Diarrhea Dyspepsia Flatulence Nausea *Other systems similar to placebo*	40-90 Avg. 62.6	M/F	1000mg qd	4 wks	Osteoarthritis	Controlled release Rx formulation of naproxen sodium has similar safety profile to OTC naproxen sodium with mainly GI system AE's observed and other system AE's similar to placebo
American Journal of Therapeutics. 2004; 11: 85-94.	A multicenter, randomized, double-blind, placebo-controlled, multi-dose, parallel-design clinical trial.	465 total 161 NAP	*GI system* Dyspepsia Nausea Diarrhea Constipation Abdominal pain GI Upset Vomiting Rectal bleeding	Avg. 60.6	M/F	440/660mg	7days	Osteoarthritis of the knee	GI events are the most common AE for naproxen sodium. For other organ systems, the safety profile of naproxen sodium was similar to placebo.

TABULAR SUMMARY OF SAFETY DATA ON NAPROXEN SODIUM

Article Citation	Study Type/ Design	Size of Study Population	Adverse Events	Age	Sex	Dose	Duration	Relevant Medical History	Comments
Clinical Therapeutics. 2001; Vol. 23, No. 9:1422-1428.	A Randomized, Double - blind, double-dummy, placebo-controlled, parallel group study Clinical Trial	17 total 4 NAP	*Digestive System* Gastroduodenal ulcers	66-75	M/F	500mg	7 days endoscopic endpoint	Relatively Healthy elderly population	Elderly patients may be at risk for GI ulceration even after short tern use of NSAID's Study terminated early due to gastric and duodenal ulcers Note small study population for NAP
British Medical Journal 2005; 331, 1310-1312.	Nested case control study	9407	Upper GI events	>25	M/F	-	4yrs	Surgery Hemorrhage Perforation Diabetes Heart Disease Hypertension Osteoarthritis	The highest odds ratio was linked with current use of naproxen, a more than double risk of a GI event, after making adjustments for potential confounding factors The risk of adverse gastrointestinal outcomes in patients taking NSAIDS was reduced by concurrent use of ulcer healing drugs.
British Medical Journal 2005; 330, 1-7	Nested case control study	9218	Study focused on increased risk for myocardial infarction	25-100	M/F	N/A	4yrs	Heart Disease	No evidence of a cardioprotective effect for naproxen sodium was found. Study did not analyze other AE's.

TABULAR SUMMARY OF SAFETY DATA ON NAPROXEN SODIUM

Article Citation	Study Type/ Design	Size of Study Population	Adverse Events	Age	Sex	Dose	Duration	Relevant Medical History	Comments
Annals of Internal Medicine. 2003; 139: 539-546.	A Randomized, Controlled Clinical trial	5557 total 2772 NAP	*Gastrointestinal disorders* Abdominal pain Nausea Diarrhea Constipation *Other:* Headache Upper respiratory infection	Avg. 63	M/F	500 mg bid	12 wks	Osteoarthritis of the knee, hip, hand or spine	8.1% of patients discontinued study due to GI side effects. Of low dose aspirin users, 9.4% taking naproxen discontinued taking the drugs. Note that trial studied daily dosing over 3 month period; not a study of long term, intermittant use.
Clinical Therapeutics. 2002; Vol. 24, No. 9: 1384-1400.	Pooled analysis of five studies	443	Headache Nausea Dizziness Back pain	>16	F	400mg 200/220mg	21-36 days	Dysmenorrhea	The majority of patients did not experience any AE's, most common AE's indistinguishable as treatment failures or genuine AE's. GI upset for naproxen (3.5%) similar to placebo (3.8%).
Cephalagia. 2002, 22, 740-748.	A randomized, double blind, placebo controlled clinical trial	915 total 300 NAP	*Body as a whole* Asthenia *Digestive System* Dry mouth Dyspepsia Nausea *Nervous System* Dizziness Somnolence	>18 avg 34.6 for NAP group	M/F	375mg	6 hrs	Acute tension-type headaches	Most common AE's were dyspesia and nausea, with no statistical significance between treatment groups (APAP and placebo).

LIST OF REFERENCES (reprints enclosed)

Bansal V, Dex T, PharmD, Proskin H, PhD, and Garreffa S. **A Look at the Safety Profile of Over- the-Counter Naproxen Sodium: A Meta-analysis.** Journal of the American Pharmaceutical Association. 2001;Vol. 41:127-138.

DeArmond B, MD, MPH, Francisco C, PhD, Lin JS, PhD et al. **Safety Profile of Over-the-Counter Naproxen Sodium.** Clinical Therapeutics. 1995; Vol.17, No. 4: 587-601.

Edwards Jayne, Moore Andrew and McQuay Henry. **Rofecoxib for dysmenorrhoea: meta-analysis using individual patient data.** BioMed Central Women's Health. 2004; 4:5.

Fleischmann R, MD, Flint K, MD, Constantine G, MD, Kolecki B., and the Naprelan Study Group. **A Double -Masked Comparison of Naprelan ® and Nabumetone in Osteoarthritis of the Knee.** Clinical Therapeutics. 1997; Vol. 19, No. 4:642-655.

Golden H, Moskowitz R. W, and Minic M. **Analgesic Efficacy and Safety of Nonprescription Doses of Naproxen Sodium Compared with Acetaminophen in the Treatment of Osteoarthritis of the Knee.** American Journal of Therapeutics. 2004; 11: 85-94.

Harris S, MD, PHD, Kuss M. BS, Hubbard R, MD, et al. **Upper Gastrointestinal Safety Evaluation of Parecoxib Sodium, a New Parenteral Cyclooxygenase-2-Specific Inhibitor, Compared with Ketorolac, Naproxen, and Placebo.** Clinical Therapeutics. 2001; Vol. 23, No. 9:1422-1428.

Hippisley-Cox Julia, Coupland Carol. **Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis.** British Medical Journal 2005; 331,1310-1312.

Hippisley-Cox Julia, Coupland Carol. **Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis.** British Medical Journal 2005; 330.

Lisse R. J, MD, Perlman M., MD, Johansson G. MD, et al. **Gastrointestinal Tolerability and Effectiveness of Rofecoxib versus Naproxen in the Treatment of Osteoarthritis. A Randomized Controlled Trial.** Annals of Internal Medicine. 2003; 139: 539-546.

Milsom I, MD, PHD, Minic M, MD, Dawood MY, MD, Akin MD, et al. **Comparison of the Efficacy and Safety of Nonprescription Doses of Naproxen and Naproxen Sodium with Ibuprofen, Acetaminophen, and Placebo in the Treatment of Primary Dysmenorrhea: A Pooled Analysis of Five Studies.** Clinical Therapeutics. 2002; Vol. 24, No. 9: 1384-1400.

Prior MJ, Cooper KM, May LG, and Bowen DL. **Efficacy and safety of acetaminophen and naproxen in the treatment of tension-type headache. A randomized, double-blind, placebo-controlled trial.** Cephalagia. 2002, 22, 740-748.

REVIEW REFERENCES

1. Anaprox DS. http://www.thomsonhc.com/pdrel/librarian

2. Li De-Kun, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. BMJ. 2003 Aug 16; 327(7411): 368 – 72.

3. Naproxen, Naproxen sodium. AHFS Drug Information 2005. www.online.statref.com

4. Naproxen. Mosby's Drug Consult, 15th ed. www.online.statref.com

5. Naproxen, NSAID. Reprotox. http://csi.micromedex.com/

6. Nielsen GL, Sorensen HT et al. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. BMJ. 2001 Feb 3; 322(7281): 266 – 270.

7. Nielsen GL, Sorensen HT et al. Danish group reanalyses miscarriage in NSAID users (letter). BMJ. 2004 Jan 10; 328 (7431): 109.

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

/s/

Karen Feibus
1/6/2006 03:47:19 PM
MEDICAL OFFICER

Andrea Segal
1/6/2006 03:56:43 PM
MEDICAL OFFICER