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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

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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

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