CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-076

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

NOV 16 1999

NDA Number:	21-076
Drug Name:	Naproxen sodium 220mg/pseudoephedrine HCl 120mg
Trade Name:	Aleve Cold and Sinus™
Sponsor:	Bayer Corporation Consumer Care Division 36 Columbia Road, P.O. Box 1910 Morristown, NJ 07962-1910 Rich Cuprys (Associate Director, Regulatory Affairs) Tel: 973-254-4673 Fax:
Date submitted:	January 28, 1999
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Drug Class:	Combination of NSAID analgesic and nasal decongestant
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/S/ 11/16/99

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CC: Original NDA # 21-076
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A. BACKGROUND INFORMATION

1. Introduction

Naproxen is a nonsteroidal anti-inflammatory drug of arylpropionic chemical class with analgesic and antipyretic activities. The mechanism of the pharmacologic properties of naproxen, though not fully understood, is suggested to be related to the inhibition of prostaglandin synthesis. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation for use as an analgesic. Naproxen was approved (NDA 17-581) in 1982 and naproxen sodium (NDA 18-164) in 1987, for a number of rheumatoid indications, as well as for the management of pain. Naproxen sodium 220mg (Aleve) was approve (NDA 20-204) for the OTC market in 1994, for the temporary relief of minor aches and pains due to common cold, backache, headache, menstrual cramps, toothache, minor pain of arthritis, and muscular aches, as well as for the temporary reduction of fever. The recommended dosing is one tablet (two tablets are allowed within one hour of the first dose) every 8 to 12 hours, not to exceed two tablets in 12 hours (not to exceed one tablet in 12 hours in elderly age $\geq$65) or exceed three tablets in 24 hours in adults and children 12 years and over.

Pseudoephedrine is an indirect acting sympathomimetic amine. It exerts its decongestant effect on nasal mucosa by stimulating adrenergic nerve endings to release norepinephrine, which acts at vascular α-receptors in the upper respiratory tract to cause vasoconstriction of nasal vessels and decongestion of swollen nasal mucosal tissue. Pseudoephedrine hydrochloride is generally recognized by OTC monograph as a safe and effective nasal decongestant in adult doses up to 240mg in 24 hours and is currently available in a number of OTC products. Pseudoephedrine hydrochloride (Sudafed) 120mg was originally approved (NDA 17-941) for OTC marketing in 1979. Sudafed-12-Hours was approved in 1991 (ANDA 73-585) for the temporary relief of nasal congestion due to the common cold, hay fever, or other upper respiratory allergies, and nasal congestion associated with sinusitis and for promoting nasal and/or sinus drainage. The recommended dosing is one tablet every 12 hours, not to exceed two tablets in 24 hours in adults and children 12 years and over.

The combination of naproxen sodium 275mg and pseudoephedrine hydrochloride 60mg has been marketed in Mexico as a prescription drug since 1993 for the

symptoms of common cold at the recommended dosage of 1 capsule every 8 hours in adults and children 12 years and over. The combination product is not currently on the market of the other countries.

The sponsor has developed a combination product as a bi-layered oral tablet containing an immediate-release layer of naproxen sodium 220mg and an extended-release layer of pseudoephedrine hydrochloride 120mg, for symptomatic treatment of cold, flu, and sinusitis. Two studies using natural cold and induced cold models were proposed to investigate the effect of the combination against placebo. At the pre-IND meeting held in October 1997, the sponsor was recommended to follow the combination policy and to incorporate a factorial design in their cold studies, to study the duration of drug effect and dose response for pseudoephedrine, and to provide a larger safety data base. At a subsequent teleconference with the sponsor at the office level, the sponsor's proposal of studying the combination against placebo using nasal obstruction as the primary efficacy parameter was accepted, provided that any claim for sinusitis-related symptoms would still need a factorial design since both active ingredients are considered contributing to that particular indication. The sponsor agreed to remove sinusitis from the indication section of the labeling. The clinical studies in this NDA submission included three pharmacokinetic trials, two clinical trials using induced and natural cold models, and a label comprehension study.

2. Drug substance and drug product

The information on drug substance and drug product is provided in detail in the chemistry review. The recommended phase 4 commitments include the modification of the product dissolution method and specifications, and re-evaluation of the loss-on-drying specification based on the new dissolution method and long-term stability data.

3. Pharmacology and toxicology

As requested by the agency, two preclinical studies were conducted: a mutagenicity study and a teratogenicity study. The combination product of naproxen sodium and pseudoephedrine hydrochloride, in a 1.2 to 2.2 ratio, was not shown to be mutagenic based on the Ames test (a bacterial reverse mutation test). The teratogenicity study in rats revealed reduced fetal weights and delated skeletal ossification at 35.2mg/kg/day of naproxen sodium (identified as maternally toxic

dose level), with or without concurrent administration of 19.2mg/kg/day of pseudoephedrine hydrochloride. There were no evidence for potentiation of fetal effect of naproxen sodium by pseudoephedrine hydrochloride.

4. Pharmacokinetics

There were three pharmacokinetic (PK) studies: a single-dose, 2-way crossover study of food effect (Study S97-049); a single-dose, 4-way crossover drug interaction study of the combination against each component (Aleve and Sudafed-12-Hours) and the coadministration of components (Study S97-050); a single-dose, 2-way crossover bioequivalence study of the commercial formulation in comparison with clinical formulation (Study S98-068).

In the food effect study, pseudoephedrine in the combination drug given under fed condition was bioequivalent to pseudoephedrine given under fasting condition, in terms of the extent of total absorption and maximum absorption. The same was observed for naproxen. However, food reduced the maximum absorption of naproxen slightly, by about 15%, and prolonged the time to reach the maximum concentration from about 1 hour to about 2 hours.

In the drug interaction study, the total and maximum absorption of naproxen was not affected by the presence of pseudoephedrine. The total and maximum absorption of pseudoephedrine (with or without naproxen), though considered basically bioequivalent, were increased by the presence of naproxen. When the combination was compared to Sudafed-12-Hours, the 90% confidence interval for the ratio of pseudoephedrine levels was 103 to 116% for AUC and 111 to 127% for C_{max}. With naproxen in the formulation, the mean increase in pseudoephedrine level was about 20%, one half of which was attributable to the formulation change (a 10% increase in pseudoephedrine when coadministration of Sudafed and Aleve was compared to Sudafed alone).

In the formulation study, the commercial formulation was shown to be bioequivalent to the formulation used in clinical trials.

There were no PK studies of multiple dose effect in this submission. Based on PK review of [redacted] AUC_{inf} after a single dose is the same as $AUC_{0\text{-}12h}$ at steady state (about 4300ng-h/mL). There was no evidence of accumulation after multiple dosing. There was

a 65% increase in C_{max} at steady state (about 460ng/mL) in comparison to C_{max} after a single dose (about 280ng/mL). C_{min} was around 240ng/mL at steady state.

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B. EFFICACY

1. Induced cold study

This was a two-center, multiple-dose, randomized, double-blind, placebo-controlled, parallel study of the combination in adult healthy volunteers inoculated with rhinovirus. Subjects were treated with the combination naproxen Na 220mg/pseudoephedrine HCl 120mg or matching placebo every 12 hours for 4 days, starting the second day after virus inoculation. The daily average severity of cold symptoms: nasal obstruction (stopped-up nose/stuffiness), headache, malaise, sneezing, runny nose, sore throat, cough, and chilliness were reported by subjects and recorded by study nurse on 0-4 categorical scales 24 hours after the morning doses. In addition, the severity of nasal obstruction was recorded by subjects at 4, 8, and 12 hours after the morning doses on the first 2 treatment days.

There were 243 subjects exposed to the test medication, 206 of whom were included in the efficacy analysis: 102 active and 104 placebo subjects. There were no statistically significant differences between the treatment groups in demographic and other baseline characteristics as well as cold symptoms. Only one third of the study population had nasal obstruction (11% with at least moderate severity) and one quarter had headache (8% of active and 5% of placebo subjects with at least moderate symptom severity) at baseline.

Statistically significant treatment differences were shown in terms of overall treatment effect during the course of treatment and in terms of peak treatment effect during the first two treatment days for nasal obstruction based on repeated measures analysis. The treatment differences in headache were shown in the first two treatment days. A majority of subjects had normal temperature during the study.

2. Natural cold study

This was a three-center, multiple-dose, randomized, double-blind, placebo-controlled, parallel study of the combination in adult patients, who had recent onset of cold symptoms including nasal obstruction identified by symptom surveillance. Subjects were treated with the combination naproxen Na 220mg/pseudoephedrine HCl 120mg or matching placebo every 12 hours for 4

days. The daily average severity of cold symptoms: nasal obstruction, headache, malaise, sneezing, runny nose, sore throat, cough, and chilliness were recorded on 0-4 categorical scales 24 hours after the morning doses. In addition, the severity of nasal obstruction was recorded at 4 and 8 hour after the initial dose, and 4, 8, and 12 hours after the second morning dose.

There were 439 subjects exposed to the test medication, 421 of whom were included in the efficacy analysis: 210 active and 211 placebo subjects. There were no statistically significant differences between the treatment groups in demographic and other baseline characteristics as well as cold symptoms. At baseline, all subjects had nasal obstruction as required by inclusion criteria. About 80% had at least moderate nasal obstruction. Slightly over one half had headache and one third had at least moderate headache. Three quarters had chilliness and only one sixth had at least moderate chilliness. Temperature was not measured at baseline or during the study.

Statistically significant treatment differences were shown in terms of overall treatment effect during the course of treatment and in terms of peak treatment effect during the first two treatment days for nasal obstruction, based on repeated measures analysis. The treatment differences in headache were shown in the first three treatment days. Fever was not evaluated in the trial.

3. Efficacy conclusion

The statistically significant treatment differences in favor of the combination over placebo was replicated in the two clinical trials. The efficacy results in conjunction with the findings of bioequivalence are considered supportive of the nasal decongestive and analgesic effect of the combination in treating cold and flu symptoms.

C. SAFETY SUMMARY

1. Safety of the combination product

a. Clinical trial safety data

There were three single-dose PK studies and 2 multiple-dose studies of cold symptoms. A total of 417 subjects were exposed to at least a single dose of the combination product, 335 of whom exposed to 8 doses in 4 days. There were also 25 subjects exposed to a single dose of Aleve 220mg and Sudafed-12-Hours administered simultaneously, 24 to a single dose of the commercial batch of the combination product, 26 to a single dose of Aleve 220mg, and 26 to a single dose of Sudafed-12-Hours.

Only two subjects, one on combination and one on placebo, were terminated before the end of the 4-day treatment due to adverse events.

About one quarter of subjects in multiple-dose studies reported at least one adverse event. The most commonly reported events were somnolence, insomnia, dizziness, dry mouth, headache, nausea, and dysmenorrhea. The only remarkable findings were that significantly more cases of dizziness, dry mouth, and insomnia were reported by subjects treated with the combination than placebo based on pooled data across the trials. Based on subgroup analysis the significant differences in adverse event reporting were only detected in female subjects who accounted for 60 to 70% of the study population.

b. Literature reports

There were no reports of drug interactions between naproxen and pseudoephedrine based on a librarian assisted literature search.

c. Post marketing surveillance

Less than 10 cases of adverse events associated with the concomitant use of naproxen and pseudoephedrine were reported to the FDA Adverse Event Reporting System to date, too few to allow a reasonable observation of any trend.

2. Safety of the components

a. Naproxen sodium

Since the approval of Aleve in 1994, there have been a number of modifications on Aleve labeling in response to the changes in reporting frequency of adverse events. Based on Dr. Leonard-Segal's review of serious reactions associated with Aleve, the reporting frequency of serious allergic reactions did not increase substantially in 1998 (2.8%) in comparison to the proportion reported during the period of 1994 to 1997 (2.0%). The effect of the new allergy warning is still pending. There were no other patterns of serious adverse events that warrant action at present time.

The life-threatening dosing level of naproxen overdose was never established. Based on the overdose data from post marketing surveillance by [redacted] in patients on prescription naproxen sodium from 1994 to 1998, it is unlikely to have serious complications in case of unintentional overdose of naproxen sodium at the OTC strengths.

b. Pseudoephedrine hydrochloride

The reporting frequency of adverse events associate with the use of pseudoephedrine or pseudoephedrine containing products is relatively low, about 3000 in the last 30 years. Most commonly reported were CNS, cardiovascular, and
gastrointestinal adverse events. The type of CNS and cardiovascular effects of pseudoephedrine appeared to be dose-limiting in cases of unintentional overdose.

3. Safety conclusion

There have been no clinical data suggesting drug interactions between naproxen and pseudoephedrine. The probability of serious complications resulting from overdose with the combinations product is predicted to be very small. The combination of naproxen sodium 220mg and pseudoephedrine hydrochloride 120mg is considered a reasonably safe product to be used over-the-counter as directed for the short-term management of cold and flu symptoms.

D. LABELING

1. Label comprehension study

The label comprehension study was conducted in 390 subjects by interviews in the shopping malls. One fourth of subjects were from the low literacy group (below ninth grade by REALM literacy test) and 30% had experience with previous use of Aleve. The label used in the study covered the major components of the labeling and was presented in a paragraph format instead of drug fact format.

The problematic areas with the understanding of labeling were identified, namely, the part of warnings written as paragraphs, the conditions for which consumers should stop the use of drug and consult a physician, and the comprehension of dosing directions in the low literacy group.

The suggested labeling changes for improvement are clustering the related symptoms for the indications, clarifying certain parts of warning section, presenting information in bullet form more frequently, and using bold face more selectively.

2. Labeling recommendation

Most of the labeling recommendations are for clarification purposes. The statements about the relief of sinus pressure and pain due to sinus condition, and promoting sinus drainage were removed because these effects were not studied clinically (would require a factorial design since both components are considered contributing).

E. BENEFITS AND RISKS

Each of the active ingredients in the proposed combination: naproxen sodium 220mg and pseudoephedrine hydrochloride 120mg, has been shown to be a safe and effective OTC product. For people with cold or flu who need both an analgesic/antipyretic and a nasal decongestant, the combination provides the dosing convenience of twice-a-day dosing for the target population.

There are potential risks associated with the use of naproxen and pseudoephedrine. The intermittent use of naproxen may lead to possible sensitization with the drug and result in serious allergic reactions. The effect of the newly implemented version of the NSAID allergy warning will be monitored to determine the need for further modification of the labeling. With the use of naproxen, the risks of major gastrointestinal and renal complications, as well as the other types of serious adverse reactions, are mostly dose- and duration-related and are expected to be higher for the population predisposed to the risk factors. The risks of serious CNS, cardiovascular, or other complications associated with the use of pseudoephedrine are also mostly dose- and duration-related and increased in the population at risk. For the proposed combination product to be used OTC as directed, the anticipated most common adverse reactions are allergic type reactions and minor complaints of gastrointestinal, nervous, and cardiovascular systems.

Overdose with pseudoephedrine may cause hallucinations, convulsions, CNS depression and death. The minor CNS and cardiovascular adverse effects of pseudoephedrine appeared to be dose-limiting in cases of unintentional overdose. The increasing trend in abuse of CNS stimulants and stimulant look-alike drugs has always been of a concern. Recently, the diversion of pseudoephedrine for the manufacture of illicit drugs has also been recognized. The combination of naproxen and pseudoephedrine may discourage the drug diversion.

In summary, the combination product naproxen sodium 220mg and pseudoephedrine hydrochloride 120mg is considered safe and effective for OTC use as directed.

F. OVERALL RECOMMENDATION

The proposed OTC marketing of the combination product naproxen sodium 220mg and pseudoephedrine hydrochloride 120mg is recommended for approval.

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II. EFFICACY REVIEW

THE FORMAT OF THE EFFICACY REVIEW

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3. Efficacy results

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A. INTRODUCTION

As mentioned in the background section at the beginning of the medical review, the division/office accepted the sponsor's proposal of studying the combination of naproxen sodium and pseudoephedrine hydrochloride against placebo, based on the consideration that the active ingredients are from different therapeutic categories and are contributing to separate indications. The pulmonary division was consulted for review of the original protocols, as well as for the efficacy review of the NDA. The pulmonary review, which had a focus on the intend-to-treat population, is enclosed for reference.

Meanwhile, this reviewer has reviewed efficacy independently with the emphasis on the efficacy eligible population. The important features of the study design, baseline symptom severity, and clinical finding are briefly summarized below. The results of the studies will be discussed at the end of the efficacy review.

B. INDUCED COLD STUDY

(Protocol S97-051, NDA volumes 1.20-1.22)

1. Study description

This was a multiple-dose, randomized, double-blind, placebo-controlled, parallel study of the combination naproxen Na 220mg/pseudoephedrine HCl 120mg conducted at two centers. The key features of the protocol are presented in the following table:

Study population	Male and female healthy volunteers age 18 to 65 with a serum neutralizing antibody titer of ≤ 1:2 to the challenge rhinovirus
Baseline procedures	Two intranasal inoculations with rhinovirus at a dose of 10-100 TCID
Treatment	The combination naproxen Na 220mg/pseudoephedrine HCl 120mg and matching placebo every 12 hours for 4 days (8 doses)
Efficacy measurements (on-site during treatment)	Nasal obstruction (stopped-up nose/stuffiness) on a 0-4 categorical scale: daily average scores recorded by nurse at baseline and 24 hours after the morning doses and scores by subjects at 4, 8, and 12 hours after the morning doses on the first 2 treatment days; cold symptoms (sneezing, runny nose, sore throat, cough, headache, malaise, and chilliness) on 0-4 categorical scales: daily average by nurse at baseline and 24 hours after the morning doses and by subjects for 6 more mornings; oral body temperature, tissue collection for nasal mucus weights, and nasal blows for viral culture at baseline and each morning during the treatment; antibody titer on day 21
Efficacy parameters	Primary: severity of nasal obstruction overall and for the first two treatment days; secondary: severity of headache and malaise

2. Demographic and other baseline characteristics

The sample population consisted of 243 subjects who received the test medication, with an age range of 18 to 59 and a mean at late twenties, 77% Caucasians, and 58% females. There were no statistically significant differences between the two treatment groups with regard to demographic and other baseline characteristics such as age, race, gender, weight, height, vital signs, and cold symptoms.

Baseline (one day post-inoculation) cold and flu symptoms are summarized in terms of the symptom severity versus treatment groups for the subset included in the efficacy analysis as shown below.

	Baseline symptom severity: % of subjects in each treatment group combination (n=102) / placebo (n=104)					
Cold Symptoms	***Absent***	***Mild***	***Moderate***	***Severe***	***Very severe***	***At least moderate***
Nasal obstruction	67 / 63	23 / 27	11 / 9	0 / 2	0 / 0	11 / 11
Headache	78 / 78	14 / 17	7 / 5	1 / 0	0 / 0	8 / 5
Malaise	85 / 87	10 / 10	4/ 3	1 / 1	0 / 0	5 / 4
Sneezing	89 /86	10 / 13	1 / 1	0 / 0	0 / 0	1 / 1
Runny nose	83 / 84	14 / 12	2 / 3	1 / 1	0 / 1	3 / 5
Sore throat	49 / 47	27 / 38	20 / 13	4 / 2	4 / 1	28 / 16
Cough	93 / 86	6 / 13	1/ 2	0 / 0	0 / 0	1 / 2
Chilliness	95 /95	4 /4	0 / 1	1 / 0	0 / 0	1 / 1

About one third of the group had nasal obstruction, one half had sore throat, less than one quarter had any of the other cold symptoms at baseline. Very small proportions of the sample population had at least moderate symptom severity in the individual cold symptoms.

3. Efficacy result of the induced cold study

a. Drug exposure and the subset for efficacy analysis

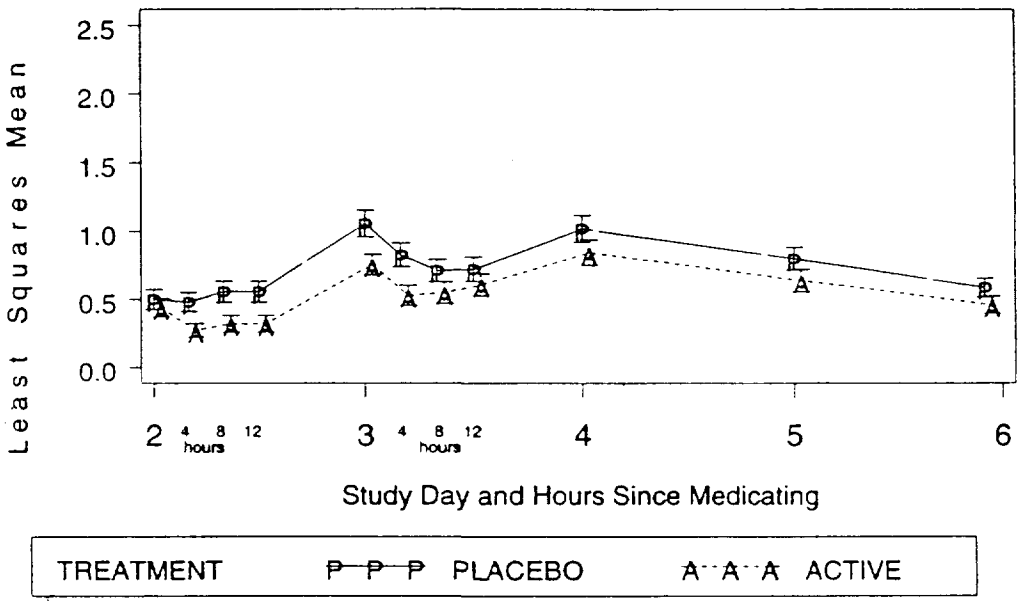
There was a total of 121 subjects exposed to the combination of naproxen Na 220mg/pseudoephedrine HCl 120mg and 122 subjects exposed to placebo. Four subjects had early termination from the study. Three of four received all 8 doses of treatment. Two dropouts were due to adverse events that occurred several days after the completion of treatment and one was due to not returning for antibody titer on day 21. One subject in the combination treatment group received only 3 doses of the treatment and then decided to withdraw from the study voluntarily.

As stated in the protocol, evidence of virus shedding for > 1 day or a 4-fold rise in antibody titer was required for inclusion in efficacy analysis. After excluding 19 subjects in the drug combination group and 18 in the placebo group for the reasons of no evidence of infection and/or failed pre-challenge titer, 102 subjects on active treatment and 104 subjects on placebo were eligible for efficacy analysis.

b. Nasal obstruction

Based on the repeated measures analysis of variance, there were no time-by-treatment interactions over treatment days 1 and 2 and over all 4 treatment days. A statistically significant overall treatment effect in favor of the combination over placebo was demonstrated ($p=0.026$ when baseline was included; $p<0.026$ for the post baseline treatment effect). Statistically significant differences, based on two-way analysis of covariance with factors of treatment, site, and baseline as a covariate, were also shown in favor of the combination over placebo at 4 ($p=0.014$) and 8 hours ($p=0.020$) after the initial dose, at 4 hours ($p=0.012$) after the second morning dose, and in terms of the average daily effect of the first treatment day ($p=0.017$). The combination performed numerically better than placebo at the rest of the evaluation time points as shown in the graph below.

Figure P-6
Mean Nasal Obstruction Scores
(LSMean + or - Standard Error, Extrapolated)
(Primary Efficacy Subjects)
(Both Sites Pooled)



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c. Cold symptoms

There were no time-by-treatment interactions in terms of headache based on the repeated measures analysis of variance over all treatment days. Statistically significant differences were shown in favor of the combination over placebo in terms of headache on treatment days 1 and 2, malaise and sneezing on treatment day 1, cough on treatment days 3 and 4, and total symptoms on days 1, 3, and 4.

The general trend in terms of mean scores over time for all secondary efficacy variables was in favor of the active treatment over placebo.

d. Fever

The mean temperatures for both the active and placebo groups were normal throughout the treatment. Only up to 7% of subjects had an oral temperature above 98.6°F and the highest temperature recorded was 101.3°F.

e. Summary

Statistically significant treatment differences were shown in terms of overall treatment effect during the course of treatment and in terms of peak treatment effect during the first two treatment days for nasal obstruction. The extended-release decongestive effect of the combination was demonstrated by statistically significant treatment difference at 8 hours after the initial dose. The non-significant separation at 12 hours after the initial dose could be explained by less than sufficient end-of dosing level before reaching steady state. The treatment differences in headache were shown in the first two treatment days. The cold symptoms in the induced cold study model were generally mild and not accompanied by fever and improved rapidly after the first 2 treatment days.

C. NATURAL COMMON COLD STUDY

(Protocol S97-052, NDA volumes 1.23-1.25)

1. Study description

This was a multiple-dose, randomized, double-blind, placebo-controlled, parallel study of the combination naproxen Na 220mg/pseudoephedrine HCl 120mg conducted at three centers. The key features of the protocol are presented in the table below:

Study population	Male and female healthy volunteers age 18 or older enrolled in a prospective symptom surveillance study who had recent (within 36 hours) onset of cold symptoms including nasal obstruction
Treatment	The combination naproxen Na 220mg/pseudoephedrine HCl 120mg and matching placebo every 12 hours for 4 days (8 doses)
Efficacy measurements (off-site, except baseline)	Nasal obstruction (stopped-up nose/stuffiness) based on a 0-4 categorical scale: daily average scores at baseline and 24 hours after the morning doses, scores at 4 and 8 hour after the initial dose, and 4, 8, and 12 hours after the second morning dose; cold symptoms (sneezing, runny nose, sore throat, cough, headache, malaise, and chilliness) on a 0-4 categorical scales: baseline and daily average after the morning doses
Efficacy parameters	Primary: severity of nasal obstruction overall and for the first two treatment days; secondary: severity of headache, malaise, sneezing, runny nose, sore throat, cough, and chilliness

2. Demographic and other baseline characteristics

The sample population consisted of 439 subjects who received the test medication, with an age range of 18 to 59 and a mean at late twenties, 77% Caucasians, and 70% females. There were no statistically significant differences between the two treatment groups with regard to demographic and other baseline characteristics such as age, race, gender, weight, height, vital signs, and cold symptoms.

Baseline cold and flu symptoms are summarized in terms of the symptom severity versus the treatment groups for the subset included in the efficacy analysis as shown below.

	Baseline symptom severity: % of subjects in each treatment group combination (n=210) / placebo (n=211)					
Cold Symptoms	***Absent***	***Mild***	***Moderate***	***Severe***	***Very severe***	***At least moderate***
Nasal obstruction	0 / 0	17 / 20	53 / 52	26 / 22	4 / 5	83 / 79
Headache	48 / 44	19 / 22	23 / 18	9 / 12	1 / 5	33 / 35
Malaise	27 / 24	25 / 27	33 / 31	11 / 13	4 / 4	48 / 48
Sneezing	35 / 31	34 / 35	24 / 25	6 / 8	0 / 1	30 / 34
Runny nose	14 / 14	30 / 33	35 / 32	20 / 19	1 / 1	56 / 52
Sore throat	14 / 18	21 / 21	34 / 36	22 / 18	8 / 8	64 / 62
Cough	38 / 37	28 / 27	24 / 26	9 / 9	1 / 2	34 / 37
Chilliness	77 / 68	11 / 17	10 / 10	1 / 4	1 / 1	12 / 15

Most (about 80%) subjects had at least moderate nasal obstruction, one third had at least moderate headache, and one half had at least moderate malaise at baseline. The other symptoms of at least moderate severity ranged from 12 to 64%.

3. Efficacy results of the natural common cold study

a. Drug exposure and the subset for efficacy analysis

There was a total of 219 subjects exposed to the combination of naproxen Na 220mg/pseudoephedrine HCl 120mg and 220 subjects exposed to placebo. Eight subjects had early termination (received partial treatment) from the study, four from each treatment group. Five more subjects in each treatment group were excluded from efficacy analysis because of the protocol deviations. The information is briefly summarized in terms of the reasons for exclusion per treatment group.

	Active (n=219)	*Placebo (n=220)*	*Total*
Rescue medication	1	3	4
Adverse events	1	1	2
Concurrent illness	1	3	4
Inappropriate enrollment	1	0	1
Non-compliance with protocol (off-schedule dosing or evaluation)	3	2	5
Lost to follow-up	1	0	1
Other (ineligible diary times)	1	0	1
Total	9	9	18

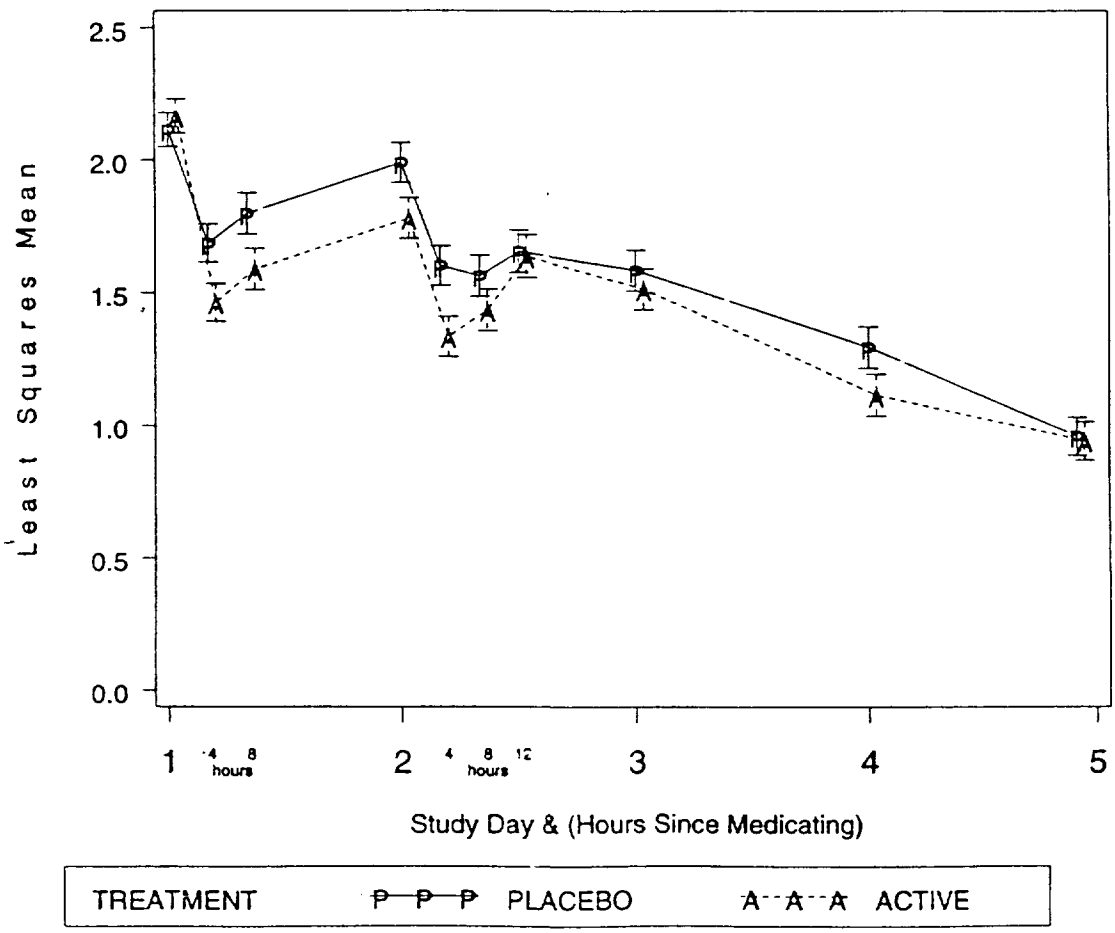
The number of subjects eligible for efficacy analysis was therefore, 210 for the combination treatment and 211 for the placebo group.

b. Nasal obstruction

Based on the repeated measure analysis of variance, there were significant time-by-treatment interactions over treatment days 1 and 2 and over all 4 treatment days. Taking the time-by-treatment interactions into the consideration, a statistically significant overall treatment effect in favor of the combination over placebo was still demonstrated over all the evaluation time points during the 4 treatment days ($p=0.043$ when baseline was included; $p=0.026$ for the after baseline treatment

effect), as well as during the first two treatment days (p=0.033 when baseline was included; p<0.033 for post baseline treatment effect). Statistically significant differences, based on two-way analysis of covariance with factors of treatment, site, and baseline as a covariate, were also shown at 4 (p=0.001) and 8 hours (p=0.004) after the initial dose, at 4 hours (p=0.001) after the second morning dose, and in terms of the average daily effect of the first treatment day (p=0.003) and the third treatment day (p=0.036).

Figure P-5.1
Mean Nasal Obstruction Scores
(LSMean + or - Standard Error, Extrapolated)
(Primary Efficacy Subjects)
(All Sites Pooled)



c. Cold symptoms

There was a significant time-by-treatment interaction in terms of headache based on the repeated measure analysis and the interaction appeared quantitative in nature. Based on a two-way analysis of covariance, statistically significant differences were shown in favor of the combination over placebo in terms of headache on the first three treatment days (p=0.001), and in terms of malaise and total symptoms on treatment day 1.

The general trend in terms of mean scores over time for all secondary efficacy variables was in favor of active treatment over placebo. There was no indication of worsening of symptoms in the active treatment group.

d. Temperature

Temperature was not measured in this trial.

e. Summary

There was a very significant overall time effect and time-by-treatment interaction due to the rapid improvement in cold symptoms. A strong evidence of treatment effect was demonstrated by statistically significant treatment differences in favor of the combination for the overall treatment effect covering all four treatment days and for the peak treatment effect during the first two treatment days in terms of nasal obstruction. The treatment differences in headache were shown in the first three treatment days. Fever was not evaluated in the trial.

D. DISCUSSION

According to the OTC drug regulations [21 CFR 330.10 (a) (4) (iv)], an OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

In addition, the general guidelines for OTC drug combination products dated September 1978 stated that: category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects.

No doubt a full factorial study design is ideal for investigating whether the individual ingredients are contributing, or whether the efficacy of the individual active ingredients is decreased by administering the drug as a combination. In this particular case, the individual ingredients are considered contributing to separate indications. The efficacy studies were designed to provide a confirmation of the PK/PD correlation, especially for the pseudoephedrine component.

There are limitations in using the induced cold and natural cold models for the evaluation of short-term multiple-dose drug effects because of the mild nature of disease and the short duration of symptoms. As observed in induced cold study, less than half of the study population had the individual symptoms and very few had a symptom of at least moderate severity at baseline. In comparison with induced cold model, there were more subjects with specific cold symptoms or with at least moderate symptom severity at baseline in the natural cold study, but the symptoms improve rapidly. The study could have been targeted at subjects with at least moderately severe nasal obstruction accompanied by at least moderately severe headache and/or fever at baseline to increase model sensitivity. A flu model might be a better choice in that regard since flu symptoms are more severe and longer lasting and are usually accompanied by fever.

To define clinical significant changes in terms of magnitude of symptom severity scores has always been a challenge, even when the changes in scores were more dramatic, based on our experience in this division.

The efficacy results for the intent-to-treat population and efficacy-eligible population appeared to be parallel to each other.

Naproxen sodium 200mg and pseudoephedrine hydrochloride 120mg, each has been shown to have both single-dose and short-term multiple-dose effects and a reasonable PK/PD correlation in the past. Naproxen sodium and pseudoephedrine hydrochloride in the combination product were shown to be bioequivalent to the components. The repeated findings of statistically significant treatment differences in favor of the combination over placebo from these clinical trials in conjunction with the findings of bioequivalence are considered substantial evidence of the nasal decongestive and analgesic effect of the combination in treating cold and flu symptoms.

E. CONCLUSION

The combination product, naproxen sodium 220mg and pseudoephedrine hydrochloride 120mg, one tablet every 12 hours, is considered efficacious for the analgesic and nasal decongestive indications in short-term management of cold and flu symptoms.

III. SAFETY REVIEW

THE FORMAT OF THE SAFETY REVIEW

A. Safety of the combination product

1. Induced cold study
    a. Study description
    b. Demographic and other baseline characteristics
    c. Safety results
        (1) Drug exposure
        (2) Adverse events
2. Natural cold study
    a. Study description
    b. Demographic and other baseline characteristics
    c. Safety results
        (1) Drug exposure
        (2) Adverse events
3. Pharmacokinetic studies
    a. Study description
    b. Adverse events
4. Overall drug exposure in clinical trials
5. Summary of clinical trial data
6. Literature reports
7. Post marketing surveillance

B. Safety of the components

1. Naproxen sodium
    a. Serious allergic reactions
    b. Overdose
2. Pseudoephedrine hydrochloride
    a. Adverse events
    b. Overdose

C. Discussion
D. Conclusion
Appendix: Tables

A. SAFETY OF THE COMBINATION PRODUCT

1. Induced cold study

(Protocol S97-051, NDA volumes 1.20-1.22)

a. Study description

This was a multiple-dose, randomized, double-blind, placebo-controlled, parallel study of the combination naproxen Na 220mg/pseudoephedrine HCl 120mg conducted at two centers. The key features of the protocol were presented in the table below:

Study population	Male and female healthy volunteers age 18 to 65
Treatment	The combination naproxen Na 220mg/pseudoephedrine HCl 120mg and matching placebo every 12 hours for 4 days (8 doses)
Safety parameters	Spontaneous reports of adverse events (AE) during and following the study

b. Demographic and other baseline characteristics

The sample population consisted of 243 subjects who received test medication, with an age range of 18 to 59 and a mean at late twenties, 77% Caucasians, and 58% females. There were no statistically significant differences between the two treatment groups with regard to demographic and other baseline characteristics such as age, race, gender, weight, height, vital signs, and cold symptoms.

c. Safety results of the induced cold study

(1) Drug exposure

There was a total of 121 subjects exposed to the combination of naproxen Na 220mg/pseudoephedrine HCl 120mg and 122 subjects exposed to placebo. Four

subjects had early termination from the study. The information on the four dropouts is summarized in terms of the treatment group, treatment duration, and the reasons for withdrawal as below.

Subject number	***Treatment***	***# doses received***	***Time of dropout***	***Reasons for dropout***
166	Placebo	8	5 days after last dose	Neck pain for 30 hours resolved with analgesics
168	Active	8	4 days after last dose	Headache for 6 hours resolved with analgesics
216	Active	8	16 days after last dose	Non-compliance (not returning for follow-up)
272	Active	3	Second day of treatment	Voluntary withdrawal

One subject in the combination treatment group received only 3 doses of treatment and then decided to withdraw from the study. Two dropouts were due to adverse events that occurred several days after the completion of treatments.

(2) Adverse events

The information on AE's per treatment group is summarized in Table 1, in terms of the number of events, number of subjects reporting, severity of events (on a scale of mild, moderate, and severe), relationship of events to study drug (based on the individual investigator's assessment), and the type of events grouped by 12 body systems.

About 25% of subjects reported at least one adverse event (AE). Among the subjects reporting, 24% were considered severe and 26% were considered study drug-related. The most frequently ($\geq$3% of subjects in either group) reported AE's were headache, insomnia, nausea, and dysmenorrhea. The body systems most frequently ($\geq$5 % of subjects) affected were body as a whole, digestive, nervous, and special senses. Majority of events were non-serious in nature. One subject on placebo had optic neuritis, which was considered serious but not as study drug-related. There were no dramatic differences between the two treatment groups with regard to the type of events, reporting frequency, severity, or relationship to the study drug.

2. NATURAL COMMON COLD STUDY

(Protocol S97-052, NDA volumes 1.23-1.25)

a. Study description

This was a multiple-dose, randomized, double-blind, placebo-controlled, parallel study of the combination naproxen Na 220mg/pseudoephedrine HCl 120mg conducted at three centers. The key features of the protocol were presented in the table below:

Study population	Male and female healthy volunteers age 18 or older enrolled in a prospective symptom surveillance study who had recent onset of cold symptoms including nasal obstructions
Treatment	The combination naproxen Na 220mg/pseudoephedrine HCl 120mg and matching placebo every 12 hours for 4 days (8 doses)
Safety parameters	Spontaneous reports of adverse events (AE) during and following the study

b. Demographic and other baseline characteristics

The sample population consisted of 439 subjects who received test medication, with an age range of 18 to 59 and a mean at late twenties, 77% Caucasians, and 70% females. There were no statistically significant differences between the two treatment groups with regard to demographic and other baseline characteristics such as age, race, gender, weight, height, vital signs, and cold symptoms.

c. Safety results of the natural common cold study

(1) Drug exposure

There was a total of 219 subjects exposed to the combination of naproxen Na 220mg/pseudoephedrine HCl 120mg and 220 subjects exposed to placebo. Eight

subjects had early termination from the study. The information on the eight dropouts is summarized in terms of the treatment group, treatment duration, and the reasons for withdrawal as below.

Subject number	***Treatment***	***# doses received***	***Type of dropout***	***Comments***
9	Active	4	Adverse events	Heart burn, palpitation, and itching. All resolved.
26	Placebo	1		Stomachache and vomiting. Both resolved
375	Active	3	Concurrent illness	Strep throat
382	Placebo	3		Non-allergic rhinitis
342	Placebo	3		Influenza
253	Placebo	1		Fever, headache, and diarrhea
526	Active	1	Lost to follow-up	
35	Active	1	Voluntary withdrawal	

Two subjects withdrew due to adverse events. One had heartburn for 1.5 hours, palpitation for 2.5 hours, and itching for 5 minutes after receiving 4 doses of active treatment. The other subject had stomachache for 14 hours and an associated short episode of vomiting after the initial placebo dose. Tums and Pepto Bismol were used by the subject for stomach pain.

(2) Adverse events

The information on AE's per treatment group was summarized in Table 2.

A total of 80 events were reported by 51 (24%) of active subjects and 57 events by 38 (17%) placebo subjects. About 8% of these events were rated as severe by active subjects and 12% by placebo subjects. And 62% of the events were considered possibly or probably study drug-related in the active treatment group and 53% in the placebo group. The most frequently (≥3% of subjects in either group) reported AE's were somnolence (5% by each group), insomnia (5% by active subjects), dry mouth (5% by active subjects), dizziness (4% by active subjects and 1% by placebo subjects), and headache (3% by placebo subjects). The body systems most frequently (≥5 % of subjects) affected were nervous (18%

active subjects and 7% placebo subjects) and body as a whole (1% active subjects and 5% placebo subjects). There were no reports of serious events. Subjects receiving active treatments had more reports of insomnia, dry mouth, dizziness, and nervous system symptoms in general than placebo subjects. There were no dramatic differences between the two treatment groups otherwise.

3. Pharmacokinetic studies in healthy volunteers

(Protocols S97-049, S97-050, and S98-068, NDA volumes 1.08-1.13)

a. Study description

The three pharmacokinetic trials were all single-center, single-dose, randomized, complete crossover studies. The information in terms of study objectives, treatments, and number of subjects exposed is summarized below.

Study number	***Study objective***	***Treatments***	***# subjects***
S97-049	Food effect	Combination product (fed) Combination product (fasted)	26 25
S97-050	Drug interaction and formulation difference	Combination product Aleve 220mg Sudafed-12-Hours 120mg, Aleve 220mg and Sudafed-12-Hours 120mg, giving together	25 26 26 25
S98-068	Bioequivalence between commercial and clinical batch	Combination product-clinical batch Combination product-commercial batch	26 24

b. Adverse events

In the food study of the combination, six subjects reported 8 events including headache, infection, pain, and diarrhea. None was considered study drug-related. There were no early dropouts due to AEs.

In the study of the combination against each component and components giving together, adverse events were reported by 9 subjects after taking drug combination,

8 subjects after Aleve 220mg, 3 subjects after Sudafed-12-Hours, and 5 subjects after taking Aleve and Sudafed together. Of the AEs (headache, pain, back pain, diarrhea, dyspepsia, gastroenteritis, tooth disorder, dysmenorrhea, urinary tract infection, syncope, and skin discoloration) reported, only headache was reported by more than one subject per treatment group. Two events were considered study drug-related. No early dropouts due to AEs.

In the bioequivalence study of the commercial and clinical batches, 7 subjects reported 11 events. All events were minor complains. None was rated severe. Six were considered possibly study drug-related. There were no early dropouts due to AEs.

4. Overall drug exposure in clinical trials

Of the 417 subjects who were exposed to at least a single dose of the combination product, 335 had completed twice daily treatments for 4 days, 25 received a single dose of Aleve 220mg and a dose of Sudafed-12-Hours given simultaneously, 24 received a single dose of the commercial batch of the combination product, 26 received a single dose of Aleve 220mg, and 26 received a single dose of Sudafed 12 hours. Placebo exposure was 342 to at least a single dose and 335 to twice daily dosing for 4 days.

5. Safety summary of clinical trial data

When the test drug was studied at low (OTC) dose levels and of short duration (not more than 4 days) of exposure, the adverse events reported were mostly minor complaints as expected. The only remarkable findings were significantly more cases of dizziness, dry mouth, and insomnia reported by subjects treated with the combination than placebo, based on the pooled data across the trials. Subgroup analysis based on gender was conducted by the sponsor. There was no treatment group difference in adverse events reported by males. The significant treatment differences in dizziness, dry mouth, and insomnia were only detected in female subjects. No elderly (age 65 or older) patients were enrolled in clinical trials.

6. Literature reports

Based on a reference librarian assisted literature search, there are only two publications on the studies of different combination products of naproxen sodium and pseudoephedrine hydrochloride. Both were Mexican studies. The first was a parallel study of the combination suspension of naproxen Na 2g and pseudoephedrine HCl 0.6g per 100mL in subjects age 2 to 16 who had common cold. The test drugs were given three times a day for 5 days. Drug exposure with respect to the treatment groups and age is summarized below.

Dose/#subjects	Age 2-5	Age 6-9	Age 10-12	Age 6-9
Combination-N/P	50mg/15mg/5subj	100mg/30mg/5subj	150mg/45mg/7subj	300mg/60mg/3subj
Pseudoephedrine	15mg/1subj	30mg/8subj	45mg/4subj	60mg/3subj
Placebo	29 subjects. (Age distribution was not provided for the placebo group.)			

The treatments appeared to be tolerated well. No adverse events were reported by any treatment group.

The second study was a single-dose, 4-way complete crossover PK trial in 20 healthy volunteers to test for bioequivalence between the combination capsule of naproxen Na 275mg and pseudoephedrine HCl 60mg and component capsules as well as the market product of pseudoephedrine HCl 60mg tablet. Adverse events were not mentioned by the author.

There are no reports of drug interactions between naproxen and pseudoephedrine in the literature.

7. Post marketing surveillance

At present time, a system for accurate and complete post-marketing monitoring for drug safety does not exist. Only limited safety information is available through the spontaneous Adverse Event Reporting System at FDA. Attempts to analyze drug safety based on the MedWatch reports could be misleading for many reasons. Not all adverse events are reported and the number of reports submitted are influenced

by the pattern of usage (intermittent versus chronic), time of approval, length of time in the market, and familiarity with or novelty of an observed adverse reaction. A given reaction may be due to underlying disease, concomitant medication, or other causes. The assessment of the causal relationship between the adverse reactions and the suspected drugs is usually not available. No information is provided on the number of patients exposed to the product for the purpose of risk ratio estimation. Nevertheless, the types of adverse events and their outcomes with respect to the concomitant use of pseudoephedrine containing products and Aleve, based on the MedWatch case reports, are summarized in Table 3.

The likelihood of the drug interaction between naproxen and pseudoephedrine can not be reasonably assessed because there was no comparison between the combination product and the components. The data base is too small to allow any observation of trends.

B. SAFETY OF THE COMPONENTS

Both naproxen sodium 220mg (Aleve) and pseudoephedrine 120mg (Sudafed-12-hours) are considered reasonably safe for OTC use and have been on the OTC market for years. An extensive safety review for either of the components is not intended by this reviewer. Important safety information considered pertinent to this review is summarized here to provide a general picture of the drug safety.

1. Naproxen sodium

a. Serious allergic reactions

Naproxen sodium 220mg was approved for OTC use in January 1994. There have been a number of labeling modification since then, based on the changes in reporting frequency of spontaneous adverse events to FDA. Stronger allergy warnings have been issued in response to the increased reports of anaphylactic and other serious allergic reactions. The details were summarized in Dr. Leonard-Segal's review. According to Dr. Leonard-Segal's analysis, the reporting frequency of serious allergic reactions did not increase substantially in 1998 (2.8% of total number of AE reports) in comparison to the proportion reported during the period of 1994 to 1997 (2.0%). The effect of the most recent revision in allergy warning is not assessable at present time because the labeling change was just implemented in March 1999.

b. Overdose

The cases of overdose by patients on prescription strengths of naproxen sodium reported to [redacted] from 1994 to 1998 are listed in Table 4 to provide a sample illustration of the type of adverse reactions and the event outcomes with respect to the extent of overdose.

The therapeutic window for naproxen as well as for NSAIDs in general is considered reasonably wide. Serious outcomes as consequences of unintentional overdose of OTC naproxen containing products are not expected.

2. Pseudoephedrine hydrochloride

a. Adverse events

Pseudoephedrine hydrochloride is one of the category I OTC monograph products and has been used alone or as an active ingredient in a number of combination drug products for many years. There were slightly over 3000 adverse events reported to the FDA Adverse Event Reporting System (AERS) since 1969. Of these events, 1562 or 50% (reporting frequency based on the total number of events) were considered serious and 129 (4% of total events) were reported as death. The most frequently reported (≥ 1%) adverse events are drug ineffective, insomnia, dizziness, headache, nervousness tachycardia, sedation, nausea, vomiting, dermatitis, dyspnea, palpitations, abdominal pain, malaise, hypertension, and asthenia.

b. Overdose

Some special overdose cases reported in the literature are selected and presented in Table 5.

There have been more than 100 case reports on pseudoephedrine overdose in FDA AERS data base. The non-duplicated cases on pseudoephedrine alone (with no concomitant drugs or other active ingredients) are summarized in terms of the type of reactions and the event outcomes with respect to the extent of overdose in Table 6.

Pseudoephedrine overdose could lead to serious consequences. In most cases of unintentional overdose in adult population, the cardiovascular and CNS adverse effects of pseudoephedrine appeared to be dose-limiting.

C. DISCUSSION

The safety profiles of naproxen and pseudoephedrine have been reasonably well known over the years of uses. The suggested dosage of naproxen sodium and pseudoephedrine hydrochloride for the drug combination is within its established safe OTC dosage range. The active ingredients in the combination were shown to be bioequivalent to the individual components. Although the pseudoephedrine component in the combination product had the 90% confidence intervals for Cmax and AUC on the upper side of the range of bioequivalence, the difference in such magnitude is not expected to be clinically significant. There was no evidence of drug accumulation in terms of the extent of exposure after repeated dosing based on previous PK data on Sudafed-12-Hours.

There have been no clinical data suggesting drug interactions between naproxen and pseudoephedrine. Short-term clinical studies at OTC dosing levels are usually of limited value in safety assessment because most adverse events are dose- and/or duration-related. The probability of serious complications resulting from overdose with the OTC combinations product is predicted to be reasonably small.

D. CONCLUSION

The combination of naproxen sodium 220mg and pseudoephedrine hydrochloride 120mg is considered a reasonably safe product to be used over-the-counter as directed, for the short-term management of cold and flu symptoms.

Table 1. Adverse events reported in the induced cold study

Summary of Adverse Events by Body System
(Both Sites Pooled)
(Page 1

	PLACEBO	ACTIVE	TOTAL
Number of Subjects	122	121	243
Number of Subjects Reporting Events	29 (24%)	32 (26%)	61 (25%)
Number of Events Reported	47	51	98
Number of Subjects Reporting			
0 Events	93 (76%)	89 (74%)	182 (75%)
1 Event	18 (15%)	20 (17%)	38 (16%)
>1 Event	11 (9%)	12 (10%)	23 (9%)
Total	122 (100%)	121 (100%)	243 (100%)
Severity of Event			
Mild	17 (36%)	25 (49%)	42 (43%)
Moderate	20 (43%)	12 (24%)	32 (33%)
Severe	10 (21%)	14 (27%)	24 (24%)
Total	47 (100%)	51 (100%)	98 (100%)
Relationship of Event to Study Drug			
Not Related	25 (53%)	24 (47%)	49 (50%)
Unlikely	12 (26%)	12 (24%)	24 (24%)
Possible	10 (21%)	15 (29%)	25 (26%)
Total	47 (100%)	51 (100%)	98 (100%)
Body System[a]			
Body as a Whole	12 (10%)	13 (11%)	25 (10%)
Allerg react	1 (1%)	0 (0%)	1 (0%)
Chills fever	1 (1%)	0 (0%)	1 (0%)
Fever	1 (1%)	0 (0%)	1 (0%)
Headache	6 (5%)	8 (7%)	14 (6%)
Pain	0 (0%)	1 (1%)	1 (0%)
Pain abdo	0 (0%)	2 (2%)	2 (1%)
Pain back	1 (1%)	1 (1%)	2 (1%)
Pain chest	1 (1%)	1 (1%)	2 (1%)
Pain neck	1 (1%)	0 (0%)	1 (0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

Table 1. (cont.)

Summary of Adverse Events by Body System
(Both Sites Pooled)
Page 2

	PLACEBO	ACTIVE	TOTAL
Body System[a]			
Digestive System	8 (7%)	7 (6%)	15 (6%)
Anorexia	1 (1%)	1 (1%)	2 (1%)
Diarrhea	3 (2%)	2 (2%)	5 (2%)
Dyspepsia	1 (1%)	1 (1%)	2 (1%)
Nausea	5 (4%)	3 (2%)	8 (3%)
Ulcer mouth	1 (1%)	1 (1%)	2 (1%)
Vomit	2 (2%)	2 (2%)	4 (2%)
Special Senses	6 (5%)	5 (4%)	11 (5%)
Conjunctivitis	1 (1%)	0 (0%)	1 (0%)
Ear dis	1 (1%)	1 (1%)	2 (1%)
Lacrimation dis	1 (1%)	0 (0%)	1 (0%)
Neuritis optic	1 (1%)	0 (0%)	1 (0%)
Pain ear	1 (1%)	3 (2%)	4 (2%)
Pain eye	1 (1%)	0 (0%)	1 (0%)
Tinnitus	0 (0%)	2 (2%)	2 (1%)
Nervous System	2 (2%)	7 (6%)	9 (4%)
Dizziness	0 (0%)	2 (2%)	2 (1%)
Insomnia	2 (2%)	5 (4%)	7 (3%)
Respiratory System	3 (2%)	4 (3%)	7 (3%)
Cough inc	1 (1%)	1 (1%)	2 (1%)
Pharyngitis	1 (1%)	1 (1%)	2 (1%)
Rhinitis	1 (1%)	2 (2%)	3 (1%)
Urogenital System	4 (3%)	2 (2%)	6 (2%)
Dysmenorrhea	4 (3%)	2 (2%)	6 (2%)
Skin	2 (2%)	3 (2%)	5 (2%)
Herpes simplex	0 (0%)	1 (1%)	1 (0%)
Pruritus	0 (0%)	2 (2%)	2 (1%)
Rash	1 (1%)	0 (0%)	1 (0%)
Sweat	1 (1%)	0 (0%)	1 (0%)
Cardiovascular System	2 (2%)	2 (2%)	4 (2%)
Anomaly vascul	1 (1%)	0 (0%)	1 (0%)
Migraine	1 (1%)	2 (2%)	3 (1%)
Musculoskeletal System	2 (2%)	2 (2%)	4 (2%)
Myalgia	2 (2%)	2 (2%)	4 (2%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

Table 2. Adverse events reported from the natural cold study

Summary of Adverse Events by Body System
(All Sites Pooled)
Page 1

	Placebo	Active	Total
Number of Subjects	220	219	439
Number of Subjects Reporting Events	38 (17%)	51 (23%)	89 (20%)
Number of Events Reported	57	80	137
Number of Subjects Reporting			
0 Events	182 (83%)	168 (77%)	350 (80%)
1 Event	26 (12%)	33 (15%)	59 (13%)
>1 Event	12 (5%)	18 (8%)	30 (7%)
Total	220 (100%)	219 (100%)	439 (100%)
Severity of Event			
Mild	24 (42%)	39 (49%)	63 (46%)
Moderate	26 (46%)	35 (44%)	61 (45%)
Severe	7 (12%)	6 (8%)	13 (9%)
Total	57 (100%)	80 (100%)	137 (100%)
Relationship of Event to Study Drug			
Not Related	8 (14%)	4 (5%)	12 (9%)
Unlikely	19 (33%)	26 (33%)	45 (33%)
Possible	28 (49%)	45 (56%)	73 (53%)
Probable	2 (4%)	5 (6%)	7 (5%)
Total	57 (100%)	80 (100%)	137 (100%)
Body System[a]			
Nervous System	15 (7%)	39 (18%)	54 (12%)
Anxiety	0 (0%)	1 (0%)	1 (0%)
Dizziness	2 (1%)	8 (4%)	10 (2%)
Dry mouth	1 (0%)	10 (5%)	11 (3%)
Euphoria	0 (0%)	2 (1%)	2 (0%)
Hyperkinesia	1 (0%)	1 (0%)	2 (0%)
Insomnia	1 (0%)	11 (5%)	12 (3%)
Nervousness	1 (0%)	3 (1%)	4 (1%)
Paresthesia	0 (0%)	1 (0%)	1 (0%)
Somnolence	10 (5%)	10 (5%)	20 (5%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

Table 2 (cont.)

Summary of Adverse Events by Body System
(All Sites Pooled)
Page 2

Body System[a]	Placebo	Active	Total
Body as a Whole	12 (5%)	3 (1%)	15 (3%)
Chills	0 (0%)	1 (0%)	1 (0%)
Fever	2 (1%)	0 (0%)	2 (0%)
Headache	6 (3%)	1 (0%)	7 (2%)
Abdominal pain	5 (2%)	1 (0%)	6 (1%)
Back pain	1 (0%)	0 (0%)	1 (0%)
Digestive System	9 (4%)	6 (3%)	15 (3%)
Constipation	0 (0%)	1 (0%)	1 (0%)
Diarrhea	1 (0%)	1 (0%)	2 (0%)
Dyspepsia	2 (1%)	3 (1%)	5 (1%)
Nausea	5 (2%)	1 (0%)	6 (1%)
Vomiting	1 (0%)	0 (0%)	1 (0%)
Respiratory System	4 (2%)	3 (1%)	7 (2%)
Epistaxis	1 (0%)	0 (0%)	1 (0%)
Hyperventilation	0 (0%)	1 (0%)	1 (0%)
Pharyngitis	0 (0%)	1 (0%)	1 (0%)
Rhinitis	3 (1%)	1 (0%)	4 (1%)
Cardiovascular System	2 (1%)	2 (1%)	4 (1%)
Migraine	2 (1%)	0 (0%)	2 (0%)
Palpitation	0 (0%)	1 (0%)	1 (0%)
Tachycardia	0 (0%)	1 (0%)	1 (0%)
Metabolic/Nutrition Disorders	1 (0%)	2 (1%)	3 (1%)
Edema	0 (0%)	1 (0%)	1 (0%)
Thirst	1 (0%)	1 (0%)	2 (0%)
Special Senses	2 (1%)	1 (0%)	3 (1%)
Conjunctivitis	1 (0%)	0 (0%)	1 (0%)
Dry eyes	0 (0%)	1 (0%)	1 (0%)
Ear pain	1 (0%)	0 (0%)	1 (0%)
Skin	0 (0%)	2 (1%)	2 (0%)
Pruritus	0 (0%)	1 (0%)	1 (0%)
Sweating	0 (0%)	1 (0%)	1 (0%)
Urogenital System	1 (0%)	1 (0%)	2 (0%)
Urine abnormality	1 (0%)	0 (0%)	1 (0%)
Urinary frequency	0 (0%)	1 (0%)	1 (0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

Table 3. Spontaneous reports of AEs in cases of concomitant use of pseudoephedrine containing products and Aleve

Age/ gender	*Drugs*	*Adverse reactions*	*Outcome*
17 F	Aleve 2 tablets taking with Sudafed 1 tablet	Facial edema	Recovered after Benadryl
24 F	Aleve 1 tablet followed by second tablet in 13 hours, taking with Advil Cold and Sinus (ibuprofen/pseudoephedrine HCl)	Dry mouth, circumoral paresthesia	Resolved after stop the drugs
26 F	Aleve 2 tablets taking with Drixoral (pseudoephedrine HCl/acetaminophen) 1 tablet	Palpitation, hand tremor, dizziness	Resolved spontaneously
29 F	Aleve 1 tablets taking with Seldane D (Pseudoephedrine HCl/terfenadine)	Insomnia	Resolved spontaneously
30 F	Aleve 2 tablets taking with Sudafed 1 tablet	Erythema/edema/itching of eyes, nose and throat	Recovered with treatment
32 F	Aleve 2 tablets taking 1.5 hours after Seldane-D 0.5 tablet and Synthroid	Dizziness, flushing	Resolved spontaneously
33 F	Aleve 2 tablets taking with Sudafed 0.5 tablet	Abdominal pain	Resolved spontaneously
40 F	Aleve 2 tablets taking with gabapentin, Seldane-D 30 minutes later (for allergic reaction)	Esophageal pain, face edema, vasodilation, asthma, urticaria	Recovered with treatment
41 F	Aleve (2 tabs/day) taking with Drixoral (pseudoephedrine sulphate /dexbrompheniramine maleate /acetaminophen/) and fresh tomato (history of allergic reaction to fresh tomato)	Rash	Recovered with treatment

Table 4. Sample cases of overdose with naproxen sodium

Age/ gender	*Naproxen Na dosing*	*Adverse reactions*	*Outcome*
3 M	Accidental ingestion of a 550mg tablet	Vomiting	Resolved
12 F	5500mg (10 tablets) in a suicide attempt	Dizziness, malaise, respiratory difficulties	Hospitalized and recovered
13 F	10 doses (strength unknown), taken [redacted]	Coma (brief), confusion, dizziness, abdominal pain	Hospitalized and recovered
16 F	5500mg, taken with 30 tabs of [redacted]	Gastric pain, vomiting, hepatitis	Hospitalized and recovered
23 M	Unknown dosing, taken with [redacted] codeine, misoprostol, and [redacted] in a suicide attempt	Creatinine phosphokinase elevation	Hospitalized and recovered
26 F	5500mg (10 tablets)	Anaphylactic shock	Hospitalized and recovered
31 F	Unknown dosing, taken with ibuprofen and alcohol in a suicide attempt	Drowsiness	Hospitalized and recovered
38 F	1650mg/day chronically	Edema	Resolved after drug was stopped
46 M	4500mg (750mgx6), taken with [redacted]	Neuritis, ascites, edema, hepatocellular damage	Recovered
54 F	1100mg/day for three days	Menstrual disorder, tinnitus, vertigo	Unknown

Table 5. Selected cases of pseudoephedrine overdose reported in the literature

Author, Journal, year	*Age/ gender*	*Pseudoephedrine dosing*	*Adverse reactions*	*Outcomes*
Salmon et al, Am J Emerg Med, Mar 99	22 M	[redacted]	Disseminated intravascular coagulation and rhabdomyolysis	Death
McCleave et al, Aust N Z J Med, Apr 78	17	unknown quantity of pseudoephedrine and choline theophyllinate in a suicide attempt	Severe hypokalemia caused by compartmental shift	Hospitalized and recovered
Loizou et al, J Neurol Neurosurg Psychiatry, May 82	17 F	Pseudoephedrine 60mgx20 (1200mg) in a suicide attempt	Intracranial hemorrhage	Hospitalized and recovered

Table 6. Spontaneous reports of pseudoephedrine overdose

Age/ gender	*Pseudoephedrine dosing*	*Adverse reactions*	*Outcomes*
1.5 F	Pseudoephedrine 30mg x20+ (>600mg)	Tachycardia, sweating, convulsion	Hospitalized and recovered
1.5 F	Sudafed 30mg x40 (1200mg)	Hypertension, tachycardia	Hospitalized and recovered
2 M	Sudafed 30mg x20-30 tabs (600-900mg)	Nervousness, buccoglossal syndrome	Hospitalized and recovered
2 M	Sudafed Children's Liquid 1 oz (~30mL or 90mg)	Tachycardia	Hospitalized and recovered
2 M	Sudafed (?strength) x60 tabs	Tachycardia	Hospitalized and recovered
3 F	Sudafed Syrup 60mg/day, x2 days	Agitation	Spontaneously resolved
7 M	Sudafed 60mg	Coma, vomiting, convulsion	Hospitalized and recovered
11 F	Sudafed-12-Hour x2 (240mg)	None	
13 F	Sudafed 60mg x8 (480mg)	Agitation, anorexia, insomnia, hallucination, manic depression	Hospitalized and recovered
17 F	Sudafed-12-Hour x2 (240mg)	None	
19 F	Sudafed-12-Hour x5 (600mg)	Somnolence	Spontaneously resolved
30 F	Sudafed-12-Hour x2 (240mg)	Tachycardia, insomnia, nervousness	Spontaneously resolved
30 F	Sudafed 30mg, 2-6 tab/day x6 years	Nervousness, anxiety, sweating, depression	Hospitalized and recovered
33 F	Sudafed-12-Hour x2 (240mg)	Insomnia, nervousness	Spontaneously resolved
35 M	Pseudoephedrine 30mg, 20 tabs/day x7 days (history of alcohol and drug abuse; history of asthma and cardiac disease)	Cardiac arrest, hypoxia, anoxic encephalopathy (asthma is contributing)	Disabled (on mechanical ventilation)
38 F	Sudafed-24-Hour x2 (480mg) in 12 hours	Nervousness	Spontaneously resolved
43 F	Sudafed-12-Hour x2 (240mg)	None	
47 M	Sudafed-12-Hour x2 (240mg)	None	
50 F	Sudafed-12-Hour x2 (240mg)	None	
82 F	Sudafed-24-Hour x3 (720mg) in 10 hours	Tachycardia, nervousness	Spontaneously resolved
Adult F	Sudafed-24-Hour x2 (480mg) in 10 hours	Nervousness	Spontaneously resolved
Adult F	Sudafed, chronic overdose	Psychosis, paranoid reaction	Hospitalized
Adult M	Sudafed-12-Hour x6 (720mg) in 8 hours	Nausea, nervousness	Spontaneously resolved