CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-076

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Naproxen Sodium 220mg & Pseudoephedrine HCl 120mg (SR) Aleve® Cold and Sinus caplets Reviewer: A. Noory NDA: 21-076	Bayer Corporation Consumer Care Division Morristown, NJ 07962 Submission Dates: Jan. 28, 1999 June 2, 1999; July 20, 1999

Review of an NDA

I. Synopsis

Bayer Consumer Care Division submitted NDA 21-076 for Aleve® Cold and Sinus caplets (Naproxen Sodium 220 mg and Pseudoephedrine HCl 120mg SR Caplets). The applicant is seeking approval for Aleve® Cold and Sinus caplets for adults as a temporary pain reliever, fever reducer, and nasal decongestant. The recommended dose is one caplet every 12 hours as needed not to exceed two caplets in a 24-hour period.

In support of Human Pharmacokinetics and Bioavailability section of the NDA, three bioavailability studies were submitted. These studies characterized the bioavailability of the combination product, Aleve® Cold & Sinus, versus commercially available products, Aleve® tablets (220 mg of naproxen sodium) and Sudafed® 12 hour caplets (120 mg of pseudoephedrine HCl). The effect of food on the bioavailability of the Aleve® Cold & Sinus and the bioequivalence between the commercial batch and the batch used in the bioequivalence trial was determined.

II. Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE III) has reviewed NDA 21-076 for Aleve® Cold and Sinus Caplets. The NDA has met the biopharmaceutics requirements and the NDA 21-076 is approvable from a biopharmaceutics standpoint.

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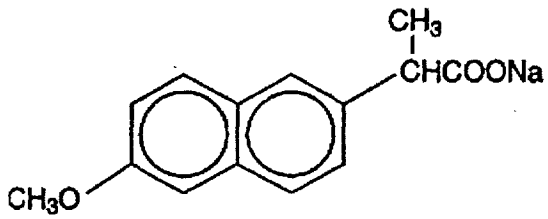
III. Background:

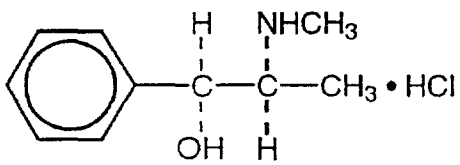
Aleve® Cold and Sinus caplets are a combination of sustained release pseudoephedrine hydrochloride (120 mg) and immediate release naproxen sodium (220 mg). Appropriate over-the-counter (OTC)

monographs cover both of these active moieties. Naproxen sodium has demonstrated analgesic, anti-inflammatory and antipyretic properties in human clinical studies. Pseudoephedrine hydrochloride is a sympathomimetic agent; it is used to relieve nasal and sinus congestion.

Naproxen sodium is a white to creamy white, crystalline powder and is freely soluble in water. The chemical name for naproxen sodium is 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, with a molecular weight of 252.25. The molecular structure is:



Pseudoephedrine hydrochloride is a white crystalline powder and soluble in water. The chemical name for pseudoephedrine hydrochloride is benzenemethanol, α-[1(methylamino)ethyl]-, [S-(R*, R*)]-, hydrochloride with a molecular weight of 201.70. The molecular structure is:



Analytical:

Formulation:

Aleve® Cold and Sinus, the combination of naproxen sodium 220 mg and pseudoephedrine hydrochloride 120 mg will be marketed as a caplet for twice daily dosing. The composition of Aleve® Cold and Sinus caplet is shown in table 1.

Table 1: Product Formulation	
Ingredient	mgs/caplet
Naproxen sodium, USP	220.00
Pseudoephedrine hydrochloride, USP	120.00
Providone, USP	[redacted]
Microcrystalline Cellulose,	
Lactose	
Hydroxypropyl Methlycellulose,	
Hydroxypropyl Methlycellulose	
Talc, USP	
Magnesium Stearate, NF	
Colloidal silicon dioxide, NF	
Total	

III. Overview of pharmacokinetic section:

The human pharmacokinetic and bioavailability section of this NDA consists of three pharmacokinetic/bioavailability studies. In these studies the applicant evaluated the bioequivalency of each active moiety of their new combination product (Aleve® C & S) to similar marketed single entity products, Aleve® and Sudafed® and demonstrated that there is no dose dumping of pseudoephedrine, the controlled release ingredient of Aleve® C & S (study # S97-050). Also the sponsor assessed the effect of food on the bioavailability of Aleve® C & S (study # S97-049). Additionally the bioequivalency of the To-Be-Marketed formulation to the clinical batch has been determined (study # S98-068).

1. **Comparative Bioavailability Study:** (Study S97-050)
   The bioavailability of the combination product, Aleve® Cold & Sinus, was compared to the commercially available, products Aleve® tablets (220 mg of naproxen sodium) and Sudafed® 12 hour caplets (120 mg of pseudoephedrine HCl). In a 4-way crossover study Aleve and Sudafed were administered separately and concomitantly along with Aleve® Cold & Sinus. The in vivo absorption profile was determined using [redacted] analysis method. This analysis confirmed that dose dumping did not occur following the administration of Aleve® Cold & Sinus. A summary of the study is located on pages 12-18 of the appendix. The graphs and the tables below show the results from this study.

Table 2: Pharmacokinetics Parameter; Study # S97-050; Mean ± SD; N=24						
PK-Parameter	Naproxen			Pseudopherine		
	Aleve C & S	Aleve	90% CI	Aleve C & S	Sudafed	90% CI
AUC(0-∞)	722.5±176.5	751.5±181.9	97.7-104.7	4680±914	4302±885	102.6-115.5
Cmax	39.43±6.62	40.49±7.02	92.7-102.3	338.8±69.75	283.2±52.77	111.4-127.4
Tmax	1.26±0.95	1.13±0.92		4.89±1.58	6.18±2.08	

Figure 1:Pseudoephedrine: Plasma Concentration Time Profile; N=24

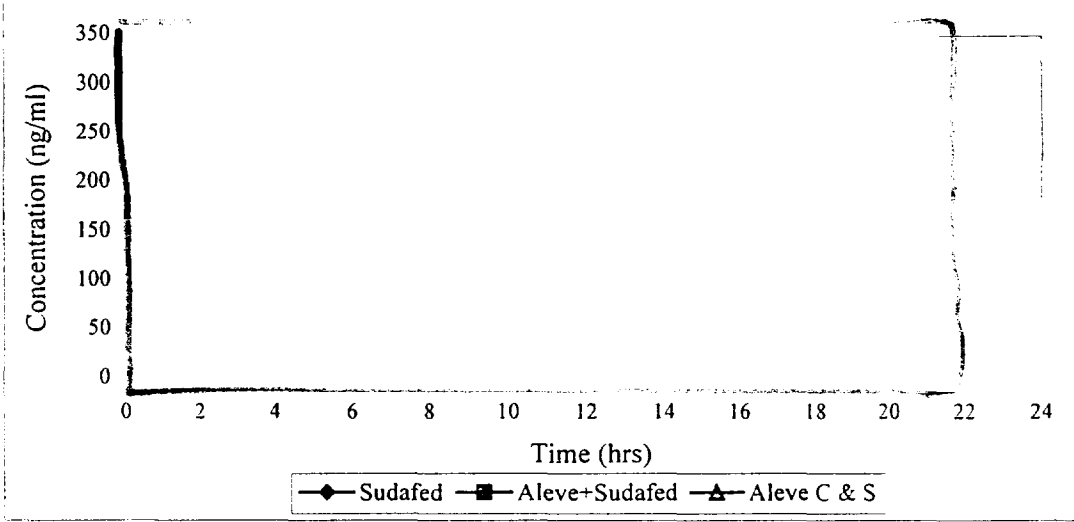


Table 3: Pharmacokinetics Parameter; Study # S97-050; Mean ± SD; N=24						
PK-Parameter	Naproxen			Pseudopherine		
	Aleve C & S	Aleve+sudafed	90%CI	Aleve C & S	Aleve+sudafed	90%CI
AUC(0-∞)	722.5±176.5	716.5±173.7	97.6-104.6	4680±914	4783±1077	92.3-103.9
Cmax	39.43±6.62	41.89±5.71	89.1-98.2	338.8±69.75	311.6±71.99	101.7-116.4
Tmax	1.26±0.95	0.75±0.29		4.89±1.58	6.09±1.59	

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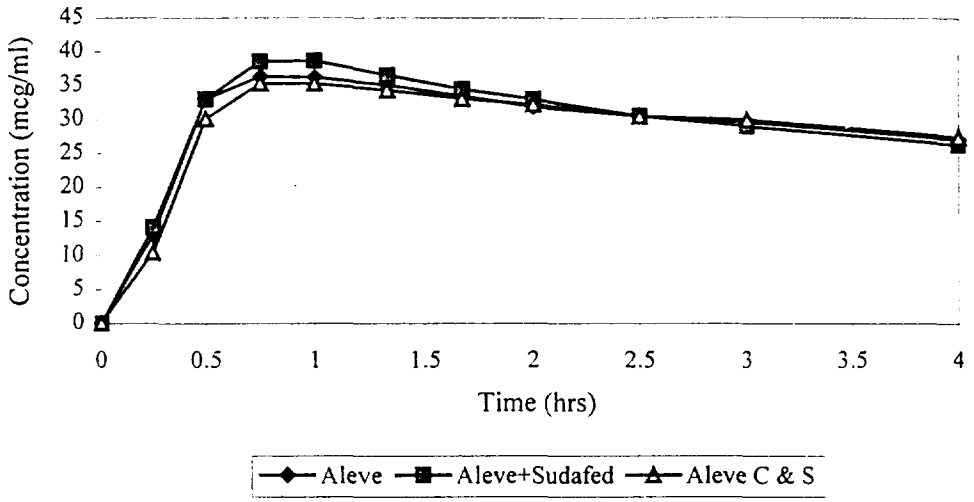
Figure 4: Naproxen; Mean Plasma Concentration; N=24



Based on the 90% confidence intervals, the naproxen sodium portion of the combination product was bioequivalent to the Aleve® with respect to AUC and Cmax. For pseudoephedrine the combination product was bioequivalent to the Sudafed® with respect to AUC. However for Cmax the 90%CI was 111.4-127.4 which is outside of the limits for bioequivalent to Sudafed (table 1 above). However when Aleve® Cold and Sinus was assessed against Sudafed and Aleve given concomitantly, both active ingredients were found to be bioequivalent (table 2 above). Additionally, based on the [redacted] profile of absorption of pseudoephedrine (figure 3 above), the absorption of the pseudoephedrine from the combination product is not much different from that of the Sudafed® keeping in mind the variability associated with the in vivo data. Furthermore, given the small difference seen, there is no expectation that an accumulation of pseudoephedrine will occur upon multiple dose administration since the half-life of pseudoephedrine is about 6 hours and the recommended dosing is every 12 hours. Examination of the data from all four treatment legs suggest that naproxen is enhancing the absorption of pseudoephedrine to a modest extent. As shown in the table 3 below, there is a 10-20% average increase in pseudoephedrine when pseudoephedrine is administered with naproxen.

Table 4: Relative Increase In Pseudoephedrine Given In Combination			
	Sudafed (alone)	Aleve and Sudafed	Aleve Cold and Sinus
C_{Max} PSE	283.2 ± 52.77	311 ± 71.77	338 ± 69.75
% increase relative to Sudafed (alone)	[redacted]	+10%	+19%

Whether this is due to the local effect of naproxen on the GI blood flow/micro-environment is unknown at this time. As Aleve® C & S is a fixed combination product, these increases should be reproducible. Discussion with the reviewing medical officer, Dr. Christina Fang, indicated that these differences should not be significant and given the fact that there is safety data from the to-be-marketed dosage form, these small differences in bioequivalence can be accepted clinically.

2. **Effect of Food:** (Study S97-049)
The effect of a high fat breakfast (OGD breakfast) on the rate and extent of absorption of the combination product (Aleve® Cold & Sinus) was investigated in this single dose crossover study. The summary of the study is located on pages 19-21 of the appendix and the results are shown in the following table and graphs.

Table 5: Effect of Food:						
PK-Parameter	Pseudoephedrine			Naproxen		
	Fasted	Fed	90%CI	Fasted	Fed	90%CI
AUC(0-∞)	4553±1333	4763±1364	95.2 – 114.9	630±110	617±108	95.2 – 100.3
Cmax	339.4±56.4	377.3±65.67	106.4 – 116.0	38.67±4.61	33.44±4.61	81.1 – 91.0
Tmax	3.85±1.53	4.24±1.94		1.04±0.60	2.17±1.59	

Figure5: Effect of Food; Pseudoephedrine N=25

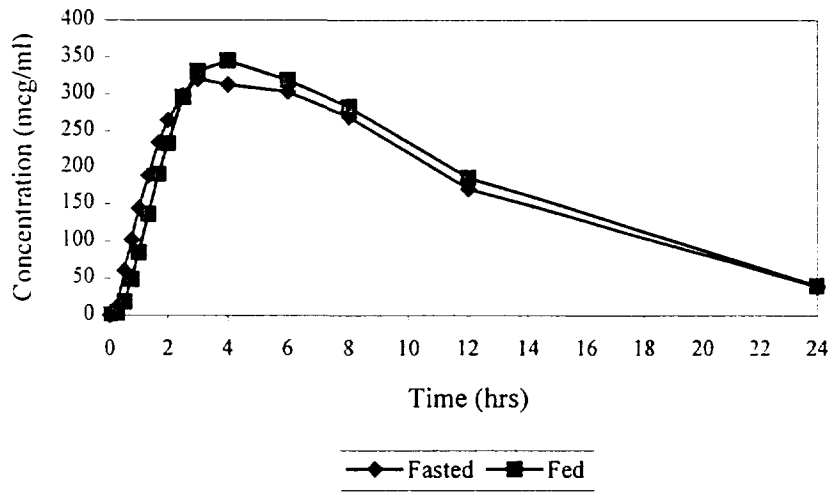
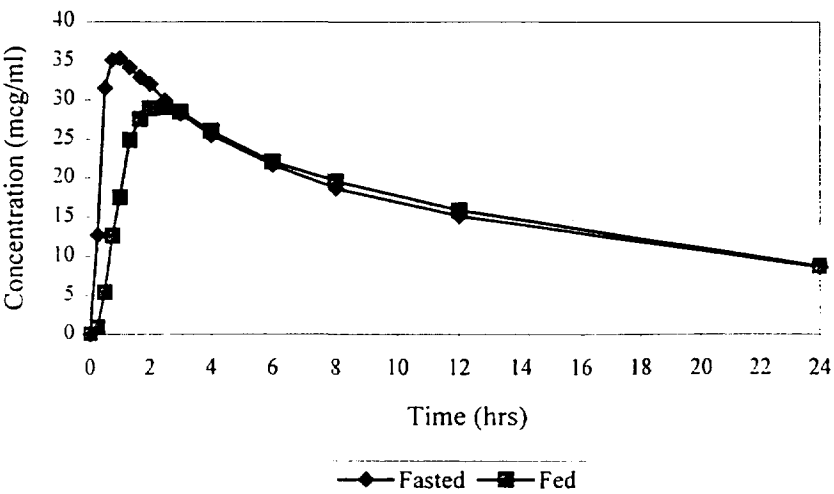


Figure 6: Effect of Food; Naproxen N=25



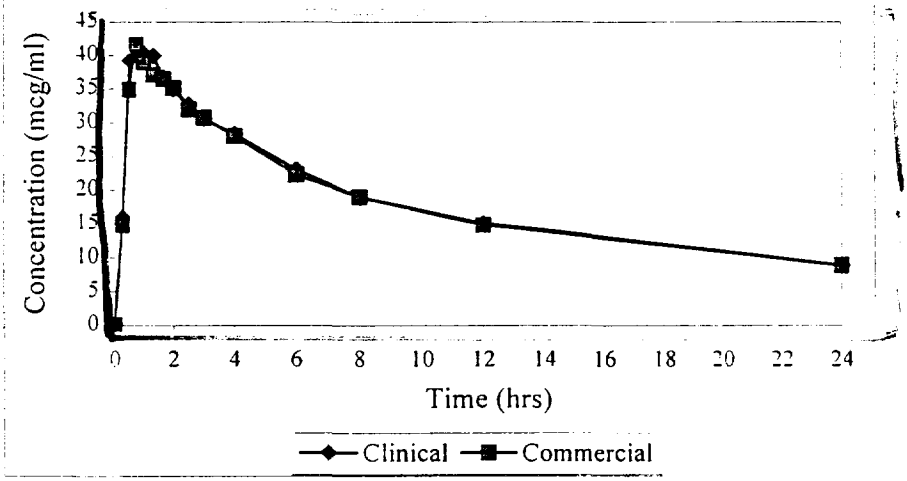
The result shows that the extent of absorption of pseudoephedrine and naproxen was not influenced with food. However the Cmax was reduced and the Tmax was prolonged for Naproxen. Both components of Aleve C & S are found to be bioequivalent under fed and fasting conditions based on the 90% confidence intervals, table 5.

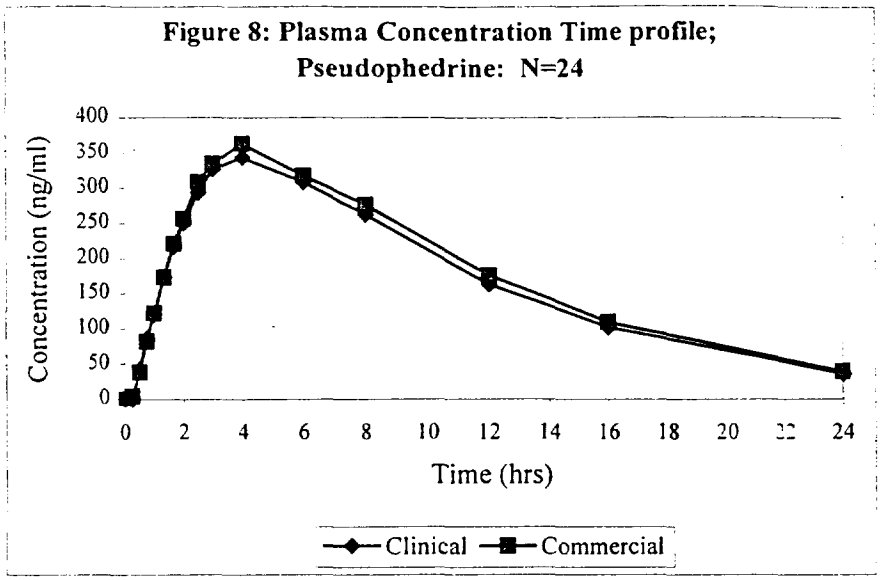
3. **Bioequivalence Study:** (Study S98-068)
The bioavailability of the to-be-marketed formulation [redacted] was compared to the batch prepared for clinical trial use (manufactured at Bayer Morristown, NJ) in a 2-way crossover bioequivalence study. A summary of the study is located on pages 22-24 of the appendix. The table and the graphs below show the result of this study.

Table 6: Bioequivalence: Commercial Lot vs. Clinical Lot; Mean ±SD; N=24

PK-Parameter	Naproxen			Pseudophedrine		
	Clinical Lot	Commercial Lot	90%CI	Clinical Lot	Commercial Lot	90%CI
AUC(0-∞)	659.5±113.8	649.2±128.5	95-101	4426±951	4689±896	100-113
Cmax	45.98±9.88	44.99±8.95	92-105	351.5±64.7	370.0±76.0	101-109
Tmax	0.88±0.32	1.00±0.51	[redacted]	3.91±0.96	3.77±0.75	[redacted]

Figure 7: Plasma concentration Time Profile; Naproxen: N=24





Based on the 90% CI, both of the components (Pseudoephedrine HCl, and Naproxen Sodium) in the commercial lot is bioequivalent to the clinical lot, table 6.

Dissolution Testing:

[redacted]

In consultation with the chemist, it was learned that the firm is planing to change the dissolution medium [redacted]

It is of concern that the release profile of pseudoephedrine from Aleve® Cold and Sinus is rather quick for a controlled release product, i.e. 60% and 95% dissolution in 1 and 3 hours respectively. While acceptable for quality control purposes, the sponsor should continue to develop a better method and specification.

/S/ 8/25/99

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Original: NDA 21-076

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