CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Product:	Advil® Allergy Sinus Caplets
Sponsor:	Wyeth Consumer Healthcare, Madison, N
NDA:	21-441
Submission Date:	9/17/02
Indication:	—
Purpose:	Response to Biopharm Comments
Reviewer:	Tapash K. Ghosh, Ph.D.

BACKGROUND

During review of the original NDA of the above product, the following comments were conveyed to the sponsor and was asked to address the issues:

1. *At the present time, Wyeth has not submitted sufficient in vitro data to support their proposed specification of NLT — in 45 minutes. Given that >99% of the ibuprofen, chlorpheniramine, and pseudoephedrine contained in this dosage form is dissolved in approximately 20 minutes, such a specification is neither discriminating nor necessary. Instead of the proposed specification, the Agency proposes the following: NLT — dissolved at 30 minutes. Wyeth is asked to either accept this proposed revision to in the in vitro dissolution, or to provide sufficient information (in both a tabular and graphical format) demonstrating the need for either their original proposed specification or an alternative.*

2. *The applicant needs to provide a scientific rationale and data at other conditions to support their choice of selecting the dissolution condition (— — for their specification purpose.*

The sponsor responded to the first issue as follows:

Wyeth Consumer Healthcare agrees with the Agency that the dissolution specification proposed in the NDA submission (Q = — in 45 minutes) can be tightened. Based on the dissolution data generated to date for the NDA stability batches (12-month stability) and the process optimization batches (3-month stability), Wyeth Consumer Healthcare does not believe that a dissolution specification of Q = — in 30 minutes is appropriate. Wyeth Consumer Healthcare proposes a dissolution specification of Q = — in 30 minutes based on the dissolution results for the — NDA stability batches, process optimization batches and the compendial/regulatory guidelines for setting dissolution specifications. Furthermore, a specification of Q = — at 30 minutes would provide some discrimination among samples with approximately 9% (as determined from the process optimization batches) of the samples requiring — dissolution testing.

Reviewer's Comment:

1. Regarding the first issue, the sponsor submitted in-depth stability data from the NDA batches and the process optimization batches, along with the guidelines established by the USP in recommending a dissolution specification for Advil Allergy Sinus Caplets. The process optimization data show a higher percent of samples that would enter Stage 2 testing than the NDA batches for any Q value. The data shows that a specification of Q = ___ would provide some discrimination among samples with approximately 9% (as determined from the process optimization batches) of the samples requiring ___ dissolution testing. Therefore, the sponsor proposes an alternate specification of Q = ___ at 30 minutes. Upon reviewing the sponsor's dissolution data and guidelines established by the USP in recommending a dissolution specification, the reviewer accepts the alternate dissolution specification of Q = ___ at 30 minutes in ___ at ___ for Advil Allergy Sinus Caplets.

2. The sponsor still has not addressed the second issue concerning scientific rationale and data at other conditions to support their choice of selecting the dissolution condition (___) for their specification purpose. However if they have submitted the information to chemistry reviewer then the chemistry reviewer should review the information.

Tapash K. Ghosh, Ph.D.
Pharmacokineticist

APPEARS THIS WAY
ON ORIGINAL

Concurrence:

E. Dennis Bashaw, Pharm.D./TL/HFD 880

CC: NDA 21, 441
HFD-550/Div File
HFD-550/CSO/Dean
HFD-880/Lazor/Selen
To DFS

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Tapash Ghosh
10/3/02 12:24:07 PM
BIOPHARMACEUTICS

Dennis Bashaw
10/7/02 03:41:43 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

Product:	Advil® Allergy Sinus Caplets
Sponsor:	Wyeth Consumer Healthcare, Madison, N
NDA:	21-441
Submission Date:	8/28/02
Indication:	[redacted]
Purpose:	Response to Biopharm Comments
Reviewer:	Tapash K. Ghosh, Ph.D.

BACKGROUND

During review of the original NDA of the above product, the following comment was conveyed to the sponsor and was asked to address the issue:

"In light of the finding that in the fed treatment, mean Tmax values were increased (~1 hour) for pseudoephedrine and chlorpheniramine, the applicant is suggested to address the effect of food an Tmax observed with pseudoephedrine and chlorpheniramine, the applicant is suggested to address the effect of food on Tmax observed with pseudoephedrine and chlorpheniramine in Advil Allergy Sinus Caplets in their proposed labeling."

The sponsor responded to the above issue as follows:

WCH notes that any label statement added to address food effect would be in direct conflict with an existing label statement. The proposed label indicates that when using the product it should be taken with food or milk if stomach upset occurs. Please note that a similar situation occurred during the review of NDA 21-374 for Advil Cold and Sinus Liquigels (ibuprofen 200 mg/pseudoephedrine HCl 30 mg). During the pre-NDA meeting of March 19, 2002, a request was made by the Biopharmaceutics reviewer for the inclusion of a label statement to address food effect on Cmax. Accordingly, a statement was added to the proposed product label directions. Subsequently, the OTC Division Reviewer asked for the removal of the added statement [redacted] *from the label directions. The Agency pointed out that "...NSAIDs (e.g., ibuprofen) may be taken with food to prevent GI upset and that this bulleted statement does not appear on currently marketed single-ingredient ibuprofen drug products (e.g., liquigel)". WCH agrees with this position and suggests that the effect of food on Tmax will not impact the safe and effective use of this product by the consumer.*

In addition, changes in Tmax are only seen for two of the three ingredients, and it would be difficult and confusing to attempt to convey these pharmacokinetic effects to the consumer. Therefore, we conclude that adding a statement to address the change in Tmax for some of the ingredients when the product is taken with food would not be appropriate.

Reviewer's Comment:

In light of the sponsor's response and to be consistent with labels of other products containing ibuprofen, pseudoephedrine and chlorpheniramine, the reviewer agrees that inclusion of information of changes of T_{max} of two out of three ingredients is not needed in the label.

Tapash K. Ghosh, Ph.D.
Pharmacokineticist

Concurrence:

E. Dennis Bashaw, Pharm.D./TL/HFD 880

CC: NDA 21, 441
HFD-550/Div File
HFD-550/CSO/Dean
HFD-880/Lazor/Selen
To DFS

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

/s/

Tapash Ghosh
10/3/02 12:08:31 PM
BIOPHARMACEUTICS

Dennis Bashaw
10/7/02 03:38:30 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	21-441
Submission Date(s):	03/01/02
Brand Name:	Advil® Allergy Sinus Caplets
Generic Name:	Ibuprofen/Pseudoephedrine/Chlorpheniramine (200mg/30mg/2 mg)
Reviewer:	Tapash K. Ghosh Ph.D.
Team Leader:	Dennis Bashaw Pharm.D.
OCPB Division:	DPEIII
ORM division:	HFD-550
Sponsor:	Wyeth Consumer Healthcare, Madison, NJ
Submission Type; Code:	3S
Formulation; Strength(s):	Caplets, Ibuprofen (200mg), Pseudoephedrine HCl (30 mg) and Chlorpheniramine maleate (2 mg)
Indication:	

1 Executive Summary

In this application Wyeth is seeking approval for the caplet dosage formulation of a triple combination of ibuprofen (200 mg), pseudoephedrine (30 mg) and chlorpheniramine (2 mg). The tablet/caplet dosage forms of the dual combination of ibuprofen and psedoephedrine are currently marketed over-the-counter (OTC) as Advil Cold and Sinus tablets/caplet and Advil Flu and Body Ache caplets by the applicant. This is the first application for a triple combination of ibuprofen, pseudoephedrine and chlorpheniramine.

The applicant adequately described the pharmacokinetics of the three active ingredients, ibuprofen, pseudoephedrine and chlorpheniramine following single dose administration of the triple combination caplets to healthy adults. The systemic exposure data demonstrated that the rate and extent of absorption of ibuprofen, pseudoephedrine and chlorpheniramine in the combination caplet was similar to that of the individual components administered separately.

The presence of food did not result in a change in the rate and extent of absorption of ibuprofen, pseudoephedrine and chlorpheniramine from the combination caplet.

However, in the fed treatment, mean *Tmax values were increased (≈ 1 hour) for pseudoephedrine and chlorpheniramine.*

1.1 Recommendation

Based on the data submitted in NDA 21-441, the application is acceptable from a clinical pharmacology and biopharmaceutics perspective provided the labeling recommendations and the comments on dissolution methodology and specifications described in section 4.5 and 5 are adequately addressed.

Comments to be conveyed to the Applicant:

1. The applicant proposed a relatively wide dissolution specification (Q = ——in 45 minutes) without any documentation on the rationale for this choice. Review of the dissolution results suggest that a tighter specification of NLT '— ,——— where Q =——; in 30 minutes as compared to the proposed ——(Q) in 45 minutes would be appropriate for ensuring lot-to-lot uniformity of the drug product. This was based on the fact that > 99% of ibuprofen, pseudoephedrine HCl and chlorpheniramine was dissolved in 20 minutes. Therefore, it is recommended that dissolution specification be tightened to Q = ——in 30 minutes.

2. The applicant needs to provide a scientific rationale and data at other conditions to support their choice of selecting the dissolution condition for their specification purpose.

/S/

Tapash K. Ghosh, Ph.D.
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Dennis Bashaw, Pharm.D.
Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

2 Table of Contents

3 Summary of CPB Findings

Introduction and Background: The three active moieties in Advil® Allergy Sinus Caplets are ibuprofen, pseudoephedrine and chlorpheniramine. Ibuprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) that also possesses analgesic, and antipyretic activity. It has been available over-the-counter (OTC) since 1984 for adults and, since 1995 for children. Pseudoephedrine hydrochloride is currently in the OTC final monograph for oral nasal decongestants for use in adults and children. Chlorpheniramine maleate is also currently in the OTC final monograph for oral antihistamines for use in adults and children. The proposed indication of the combination caplet is for

The combination of an analgesic, decongestant, and antihistamine is considered a Category I combination according to the Tentative Final Monograph for Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Combination Drug Products (TFM 53 FR30522). There are numerous three-ingredient combination products containing an analgesic/decongestant/antihistamine currently marketed OTC. However, these products contain acetaminophen as the analgesic component. The sponsor has developed an analgesic/ decongestant/antihistamine product containing 200 mg ibuprofen, 30 mg pseudoephedrine, and 2 mg chlorpheniramine/caplet. This proposed combination will provide consumers with the first ibuprofen-containing product designed to treat the entire spectrum of symptoms typically experienced with allergy and sinusitis.

Antihistamines effectively treat symptoms related to allergic rhinitis, including sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes. Decongestants effectively treat nasal congestion by vasoconstrictive effect on the mucous membranes in the upper respiratory tract. Administration of a decongestant promotes vasconstriction and decreases nasal airway resistance, which often accompanies the histaminic symptoms of allergy. Therefore, antihistamines are often prescribed concomitantly with decongestants, such as alpha-adrenergic agonists (e.g., pseudoephedrine). Other symptoms such as headaches, and facial pain, pressure or discomfort frequently accompany allergic episodes. Analgesics such as ibuprofen provide effective relief from these symptoms. Combination products can provide effective relief from multiple bothersome symptoms of allergy and sinusitis without the inconvenience of taking multiple drugs. According to federal regulation [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 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 support of this NDA, the sponsor conducted one **clinical study** entitled "ADVIL MULTI-SYMPTOM ALLERGY SINUS EFFICACY AND SAFETY STUDY" (Study AD-99-02, Phase of Development: III, February 13, 2001 – July 11, 2001) which was a

Multicenter 49 sites), outpatient, multiple-dose, placebo-controlled, double-blind, double-dummy, parallel group, randomized trial comparing the following treatment arms:

- Two Advil Multi-Symptom Allergy Sinus caplets (2 x ibuprofen 200 mg/ pseudoephedrine hydrochloride 30 mg/ chlorpheniramine maleate 2 mg) + One Allerest Maximum Strength placebo tablet

- One Advil Multi-Symptom Allergy Sinus caplet (1 x ibuprofen 200 mg/ pseudoephedrine hydrochloride 30 mg/ chlorpheniramine maleate 2 mg) + One Allerest Maximum Strength placebo tablet + One Advil Multi-Symptom Allergy Sinus placebo caplet

- One Allerest® Maximum Strength tablet (1 x pseudoephedrine hydrochloride 30 mg/ chlorpheniramine maleate 2 mg) + Two Advil Multi-Symptom Allergy Sinus placebo caplets

- Two Advil Multi-Symptom Allergy Sinus placebo caplets + One Allerest Maximum Strength placebo tablet

The primary objective of this study was to demonstrate the contribution of ibuprofen to the overall and/or analgesic effectiveness of buprofen/pseudoephedrine/chlorpheniramine in relieving the symptoms of SAR. (seasonal allergic rhinitis). The study also evaluated and compared the analgesic/decongestant/antihistaminic efficacy of ibuprofen/ pseudoephedrine hydrochloride/ chlorpheniramine maleate (total dose 400/60/4 mg or 200/30/2 mg), pseudoephedrine/chlorpheniramine 30 mg/2 mg and placebo in relieving the symptoms of seasonal allergic rhinitis (SAR). An additional objective of the study was to determine: a) the minimum effective dose of the combination and b) the minimum effective dose of the antihistamine component of the combination.

The study will be reviewed in detail by the medical officer. According to the sponsor, the results of this study demonstrate:

- Significant analgesic/decongestant/antihistaminic efficacy of ibuprofen/peudoephedrine/chlorpheniramine (200/30/2 mg – 400/60/4 mg) in the treatment of seasonal allergic rhinitis;

- Ibuprofen contributes to the overall effectiveness of the combination by not only relieving allergy–associated pain but also by reducing the severity of other seasonal allergic rhintis symptoms, as I/P/C 200/30/2 mg was better than P/C 30/2 mg for most assessments;

- A 2 mg dose of chlorpheniramine is effective as an antihistamine, as both I/P/C 200/30/2 mg and P/C 30/2 mg were more effective than placebo in relieving the histamine-mediated symptoms of seasonal allergic rhinitis.

- Both doses of I/P/C were equally efficacious;

- All treatments were well tolerated and the incidence of adverse experiences were consistent with those reported for similar medications containing the same doses of pseudoephedrine and chlorpheniramine. The proposed dose of I/P/C is 1-caplet every four to six hours - not to exceed 6 caplets in a 24-hour period - since both doses of I/P/C were equally effective and the 2-caplet I/P/C dose demonstrated an increased incidence of somnolence, dry mouth and asthenia relative to the 1-caplet dose. This dosing will allow for the product to be taken prior to bedtime and/or during the night (in addition to daytime dosing) and is consistent with the approved OTC daily dose of ibuprofen (1200 mg), and is still below the monograph daily doses of pseudoephedrine (240 mg) and chlorpheniramine (24 mg).

Clinical Pharmacology: This NDA is supported by two pharmacokinetic studies (AD-99-01 and AD-99-03). In the pharmacokinetic studies, analysis for ibuprofen was done by high performance liquid chromatography with ultraviolet detection, analysis for pseudoephedrine was done by LC/MS/MS and analysis for chlorpheniramine was done using ——— with ——— All these methods were found to be reproducible and accurate and, therefore acceptable for the intended use.

Study AD-99-01 was a four-way crossover study to investigate the potential for a drug-drug interaction to occur and compared the rate and extent of absorption of ibuprofen, pseudoephedrine and chlorpheniramine from the to-be-marketed Advil® Allergy Sinus combination Caplets (ibuprofen 200 mg/pseudoephedrine HCl 30 mg/ Chlorpheniramine maleate 2 mg) to currently marketed Nuprin© Tablets (Ibuprofen 200mg), Sudafed Nasal Decongestant Tablets (pseudoephedrine HCl 30 mg) and Chlor-Trimeton® 4 hour Allergy Tablets (chloepheniramine maleate 4 mg per tablet) in healthy adults under fasted condition. The results of this study demonstrated that the rate and extent of absorption of ibuprofen, pseudoephedrine HCl and chlorpheniramine maleate from the combination caplet were similar to those obtained for the individual components from the currently marketed products of single ingredients mentioned above. However, according to the regulations (21 CFR 320.25 (g)), this study should have been done as a two-way crossover with the test product compared to the concurrent administration of three separate singe entity products. Under this scenario if a drug-drug interaction occurred the sponsor would then do the more elaborate four way cross-over study to define the interaction. In doing this more definitive study instead of the "regulatory" study the sponsor was able to meet the required informational need and thus meet the intent of the regulations in a manner satisfactory to the Office of Clinical Pharmacology and Biopharmaceutics.

Study AD-99-03 was a single dose food effects study of the combination caplet. The results indicated that food did not alter the rate and extent of absorption of ibuprofen, pseudoephedrine and chlorpheniramine. However, for both pseudoephedrine and chlorpheniramine, T_{max} increased by about an hour under fed condition.

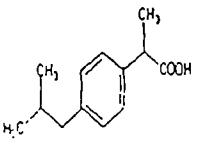
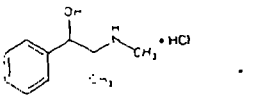
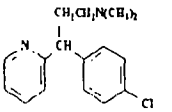
The applicant proposed a relatively wide dissolution specification (Q = ——— in 45 minutes) without any documentation on the rationale for this choice. Review of the dissolution results suggest that a tighter specification of NLT——— ,——— where Q = ——— in 30 minutes as compared to the proposed——— ,Q) in 45 minutes would be appropriate for ensuring lot-to-lot uniformity of the drug product. This was based on the fact that > 99% of ibuprofen, pseudoephedrine HCl and chlorpheniramine was dissolved in 20 minutes. Therefore, it is recommended that dissolution specification be tightened to Q = ——— in 30 minutes.

4 Review

4.1 General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substances, and formulation of the drug product?

A. Highlights of the chemistry and physical-chemical properties of the drug substances in Advil® Allergy Sinus Caplets are as follows:

Drug Name	Ibuprofen	Pseudoephedrine hydrochloride	Chlorpheniramine maleate
			
Chemical Name	(±)-2-(p-isobutylphenyl) propionic acid	Benzenemethanol, α-[1 (methylamino) ethyl]-,[S-(R*, R*)]-,hydrochloride	(±)-3-(4-chlorophenyl)-NN-dimethyl-3-(2-pyridyl)-propylamine hydrogen maleate
Molecular formula	$C_{13}H_{18}O_2$	$C_{10}H_{15}NO.HCl$	$C_{10}H_{19}ClN_2$, $C_4H_4O_4$
Molecular weight	206.29	201.70	274.80
pKa	5.4 (weak acid)	9.22 (weak base)	
pH	Between 3.6 and 4.6	4.6 -6.0 for a 5% solution in water	5 for a 2% solution in water
Description	White or almost white powder or crystals with a characteristic odor.	Fine, white to off-white crystals or powder having a faint, characteristic odor	Fine, white to off-white crystals or powder having a faint, characteristic odor
Solubility	Low solubility in water, Soluble in alcohol, acetone and chloroform. Soluble in an aqueous solution of alkali hydroxides and carbonates.	Soluble (1 g in 0.5 mL water, 3.6 mL alcohol, 91 mL chloroform, 7000 mL ether	Solubility (160 mg/ml in water, 330 mg/ml in ethanol, 240 mg/ml in chloroform and 130 mg/ml in methanol)

B. The proposed ibuprofen/pseudoephedrine/chlorpheniramine product was developed under IND 61,725. Clinical studies have been conducted using caplets (Ibuprofen 200

mg, Pseudoephedrine Hydrochloride 30 mg and Chlorpheniramine Maleate 2 mg) that are comparable to the proposed market formulation. The proposed market formulation was utilized to manufacture the NDA batches. Minor differences exist between the clinical supplies and the proposed formulation. However, these differences were not likely to impact the bioavailability, chemical and dissolution data.

	WH-0899-0005 Studies AD – 99-01, -02, -03	WH-0899-0006 NDA Batches and Proposed Market Product
Active Ingredients	mg/caplet	mg/caplet
Ibuprofen USP	200	200
Pseudoephedrine HCl USP	30	30
Chlorpheniramine Maleate USP	2	2
Inactive Ingredients		
Silicon Dioxide Colloidal NF		
Silicon Dioxide NF		
Croscarmellose Sodium NF		
Glyceryl Behenate NF		
Hydroxypropyl Methylcellulose (Hypromellose) USP		
Microcrystalline Cellulose NF		
Microcrystalline Cellulose NF		
Starch, Pregelatinized NF		
Water Purified USP [A]		
Corn Starch NF		
Carnauba Wax NF		
Total Weight		

What is the proposed dosage and route of administration?

Adults: One caplet every 4-6 hours while symptoms occur. Do not take more than 6 caplets in any 24-hour period unless directed by a doctor.

Children under 12 years of age: consult a doctor

What is the proposed mechanism of drug action and, therapeutic indications?

A. Proposed mechanism of drug action(s):

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The exact mechanism of action of NSAIDs is not known, but anti-inflammatory effects are believed to be secondary to inhibition of synthesis and/or release of prostaglandins. Ibuprofen probably has a peripheral rather than central action as an analgesic. Antipyretic activity may be due to

action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation.

Pseudoephedrine is a sympathomimetic agent with decongestant properties. Pseudoephedrine acts directly on both alpha- and, to a lesser degree, beta-adrenergic receptors. By acting directly on alpha-adrenergic receptors in the mucosa of the respiratory tract, pseudoephedrine produces vasoconstriction, which shrinks swollen nasal mucous membranes, reduces tissue hyperemia, edema, and nasal congestion; and increases nasal airway patency.

Chlorpheniramine is a classical H_1-receptor antagonist (antihistamine) which has been available for more than 40 years as a nonprescription medication for relief of allergic rhinitis symptoms. It has been shown to be effective against major histamine-mediated symptoms, i.e., sneezing, itching and ~~rhinorr~~hea.

B. Therapeutic Indications:

The proposed indications for Advil® Allergy Sinus Caplets are

- Sneezing
- Headache
- Itchy, watery eyes
- Itching of the nose and throat
- Minor aches and pains
- Nasal congestion
-

4.2 General Clinical Pharmacology

Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the active moieties, ibuprofen, pseudoephedrine and chlorpheniramine were appropriately identified and measured.

What are the pharmacokinetic parameters of ibuprofen, pseudoephedrine and chlorpheniramine in Advil® Allergy Sinus Caplets?

Reproduced in the Tables below are the pharmacokinetic parameters for ibuprofen obtained in Study AD-99-01 (relative bioavailability study) and Study AD-99-03 (food-effects study)

Table 1. Key Ibuprofen PK Parameters: Mean (S.D.) and 90% Confidence Interval (CI) (AD-99-01)

	AUCL (mcg.h/mL)	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)	T½ (h)
Treatment A	112.01 (20.74)	114.00 (21.54)	32.71 (8.46)	1.84 (0 88)	1.89 (0.34)
Treatment B*	115.50 (23.40)	119.78 (24.28)	35.47 (8.51)	1.88 (1.16)	1.99 (0.37)
(A/B*)%^	97.04	94.79	92.00		
90%CI^	92.44-101.86	90.75-99.00	84.67-99.97		

A: Advil Multi-Symptom Allergy Sinus Caplets
B: Nuprin Tablets
*: Reference treatment

Table 2. Key Pseudoephedrine PK Parameters: Mean (S.D.) and 90% Confidence Interval (CI) (AD-99-01)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Treatment A	1842.55 (374.00)	1870.14 (375.30)	236.04 (53.81)	1.69 (0.72)	4.84 (0.85)
Treatment C*	1769.50 (444.69)	1800.80 (450.53)	231.46 (57.90)	1.71 (0.73)	4.85 (0.94)
(A C*)%^	106.28	105.98	103.08		
90%CI^	101.32-111.48	101.15-111 06	98.96-107.37		

A: Advil M ulti-Symptom Allergy Sinus Caplets
C. Sudafed Nasal Decongestant Tablets
*: Reference treatment
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 3. Key Chlorpheniramine PK Parameters: Mean (S.D.) and 90% Confidence Interval (CI) (AD-99-01)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Treatment A	150.31 (60.15)	179.86 (114.98)	7.79 (2.31)	3.10 (1.04)	21.06(15.90)
Treatment D*	140.73 (48.13)	162.47 (70.85)	7.27 (1.94)	3.40 (1.56)	20.58 (9.18)
(A D*)%^	104.88	105.04	106.37		
90%CI^	99.06-111.05	98.84-111.62	101.13-111.88		

A: Advil M ulti-Symptom Allergy Sinus Caplets
D: ChlorTrimeton 4 Hour Allergy Tablet
*: Reference treatment
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 4: Key Ibuprofen Pharmacokinetic Parameters (Mean ± SD and 90% CI (AD-99-03)

Treatment	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)
Fasted (A*)	128.39 (18.42)	32.25 (5.65)	1.73 (0.93)
Fed (B)	117.19 (23.76)	29.48 (9.72)	1.57 (0.84)
(B/A)% ^	90.41	88.64	
90% CI^	87.11-93.84	79.29-99.09	

*:Reference formulation;
^ Based on the fitted log-transformed data

Table 5: Key Pseudoephedrine Pharmacokinetic Parameters (Mean ± SD and 90% CI) (AD-99-03)

Treatment	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)
Fasted (A*)	2065.89 (414.56)	223.75 (44.14)	1.52 (0.59)
Fed (B)	1997.17 (589.80)	206.25 (45.21)	2.80 (1.36)
(B/A)% ^	94.89	92 06	
90% CI^	88.73-101.47	84.34-100.48	

*: Reference formulation;
^ Based on the fitted log-transformed data

Table 6: Key Chlorpheniramine Pharmacokinetic Parameters (Mean ± SD and 90% CI) (AD-99-03)

Treatment	AUCI (ng..h/mL)	Cmax (ng/mL)	Tmax (h)
Fasted (A*)	202.55 (103.47)	8.00 (3.25)	2.88 (0.86)
Fed (B)	196.26 (88.77)	6.97 (1.93)	3.94 (1.95)
(B/A)% ^	98.94	89.56	
90% CI^	92.72-105.58	83.40-96.17	

*: Reference formulation;
^ Based on the fitted log-transformed data

The mean PK parameters obtained for ibuprofen, and chlorpheniramine between studies are similar for healthy adults when the variability associated with the values of the parameters are taken into account.

What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Was not performed

4.3 Intrinsic Factors

What intrinsic factors influence exposure?

Gender: For all three active ingredients, statistically significant ($p \leq 0.10$) gender effects and/or treatment-by-gender interactions were seen for several pharmacokinetic parameters in study AD-99-01 (relative bioavailability study). To examine if these effects/interactions were due to men generally weighing more than women, per protocol, Vd and Cl were adjusted for the subject's body weight and then analyzed statistically. Some of the gender effects and treatment-by-gender interactions remained significant after weight adjustment, suggesting that these effects/interactions were not due solely to weight differences between men and women. Therefore, the pharmacokinetic parameters were analyzed within each gender as summarized below.

Table 7. AD-99-01 Primary PK Parameters by Treatment and Gender: Mean (S.D.), Ratio, and 90% Confidence Interval (CI)

			AUCI (mcg.hr/mL)	Cmax (mcg/mL)
	Male	A Mean (SD)	107 94 (23 48)	29.65 (8 85)
Ibuprofen				
		B Mean (SD)	119 96 (30 34)	33 57 (10 97)
		(A/B*)% ^	90 05	89.94
		90% CI ^	85.16 - 95.22	76.92 - 105.17
	Female	A Mean (SD)	119 26 (18 93)	35.36 (7 40)
		B Mean (SD)	119.63 (19.28)	37.12 (5.50)
		(A/B*)% ^	99.74	94.23
		90% CI ^	93.06 - 106.89	86.42 - 102.75
			AUCI (ng.hr/mL)	Cmax (ng/mL)
	Male	A· Mean (SD)	1663.86 (234.60)	197.38 (28.45)
Pseudoephedrine				
		C· Mean (SD)	1626 18 (430 63)	185 00 (14 47)
		(A/C*)% ^	107.03	106.59
		90% CI ^	100.81 - 113.63	98 83 - 114.96
	Female	A Mean (SD)	2048 91 (388.22)	269.53 (47.96)
		C Mean (SD)	1952.13 (423 85)	271.73 (50.44)
		(A/C*)% ^	105 98	99.70
		90% CI ^	99 17 - 113 27	94.40 - 105 30
			AUCI (ng.hr/mL)	Cmax (ng/mL)
	Male	A: Mean (SD)	144 53 (35.40)	6.92 (1.13)
Chlorpheniramine				
		D: Mean (SD)	149.48 (46 82)	6.48 (1.13)
		(A/D*)% ^	97 56	104 52
		90% CI ^	88.03 - 108 12	98 19 - 111.27
	Female	A Mean (SD)	210.47 (149 19)	8 55 (2.81)
		D Mean (SD)	173 73 (S6 66)	7 95 (2 26)
		(A/D*)% ^	113 21	107.17
		90% CI ^	104 17 - 123 04	98 71 - 116 36

A· Advil M ulti-Symptom Allergy Sinus Caplets
B Nuprin Tablets
C: Sudafed Nasal Decongestant Tablets
D· Chlor-Trimeton 4 Hour Allergy Tablets *. Reference treatment
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported

Within *females*, ibuprofen, pseudoephedrine, and chlorpheniramine were absorbed at the same rate and to the same extent (based on Cmax and AUCI) from Advil Multi-Symptom Allergy Sinus relative to the reference treatments, with confidence intervals that fell within the accepted bioequivalence limits. Within *males*, pseudoephedrine, and chlorpheniramine were absorbed at the same rate and to the same extent (based on Cmax and AUCI) from Advil Multi-Symptom Allergy Sinus relative to the reference treatments, with confidence intervals that fell within the accepted bioequivalence limits. However, for *ibuprofen*, the extent of absorption from Advil Multi-Symptom Allergy Sinus was same to the reference treatment, but the *rate of absorption* (based on Cmax) was not same as 90% confidence limit was 76.92-105.17% which did not meet the accepted bioequivalence criteria. However, this difference was not clinically significant.

In addition, a significant treatment-by-gender interaction ($p \leq 0.10$) for *pseudoephedrine* AUCI and C_{max} was observed in study AD-99-03 (Food effects study). The results obtained for the female subgroup were consistent with those of the entire population. The

key findings for males and females are summarized in Table 8 and Table 9 respectively. However, despite the small sample size of this subgroup (n=6), both AUCI (CI = 77-100%) and C_{max} (CI = 75-110.8%) barely missed the accepted no food effect criteria of CI 80 – 125% for both. Again, this difference was not clinically significant.

Table 8: Pseudoephedrine Pharmacokinetic Parameters (Mean, SD, and 90% CI for Males Only (n=6)

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)	$T_{½}$ (h)
Fasted (A*)	1804.11 (221.12)	1834.01 (225.85)	199.17 (37.22)	1.33 (0.75)	5.44 (0.80)
Fed (B)	1584.06 (261.47)	1613.07 (257.56)	179.50 (21.38)	2.38 (0.97)	5.09 (0.70)
(B/A)% ^	87.37	87.59	91.01		
90% CI^	76.66-99.58	76.87-99.80	74.79-110.77		

*: Reference formulation; ^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means are reported.
Note: FDA Draft Guidance 'Food-Effect Bioavailability and Bioequivalence Studies' states that confidence intervals within 80%-125% for Ln AUCI and 70%-143% for Ln Cmax are indicative of no food effects

Table 9: Pseudoephedrine Pharmacokinetic Parameters (Mean, SD, and 90% CI for Females Only (n=6)

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)	$T_{½}$ (h)
Fasted (A*)	2267.24 (446.96)	2297.77 (445.02)	248.33 (38.08)	1.71 (0.33)	4.38 (0.41)
Fed (B)	2352.23 (595.51)	2381.27 (587.28)	233.00 (48.20)	3.22 (1.65)	4.37 (0.64)
(B/A)% ^	102.83	102.79	93.11		
90% CI^	92.96-113.75	93.24-113.32	85.97-100.84		

*: Reference formulation; ^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means are reported.
Note: FDA Draft Guidance 'Food-Effect Bioavailability and Bioequivalence Studies' states that confidence intervals within 80%-125% for Ln AUCI and 70%-143% for Ln Cmax are indicative of no food effects

Race: No statistical analysis using race as a covariate was performed by the sponsor probably due to the fact that for both studies, the number of subjects in each racial group was insufficient to conduct any meaningful analysis.

4.4 Extrinsic Factors

Is there any systemic interaction between ibuprofen, pseudoephedrine and chlorpheniramine when the drugs are administered in combination as a Caplet?

No

4.5 General Biopharmaceutics

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Key pharmacokinetic parameters for ibuprofen, pseudoephedrine, and chlorpheniramine under fed and fasted conditions are summarized in previous Tables 4, 5 , and 6 respectively. Based on Agency specified bioequivalence criteria, the results showed that the absorption of ibuprofen, pseudoephedrine, and chlorpheniramine from Advil Multi-Symptom Allergy Sinus caplets was not affected by the administration of food. However, in the fed treatment, mean *Tmax values were increased (≈ 1 hour) for pseudoephedrine and chlorpheniramine.*

Do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The proposed dissolution method and specifications used for the Advil Allergy Sinus Caplets is reproduced in the Table below:

Table 10: Dissolution Method and Specifications

Apparatus	USP Apparatus 2 Type- Paddles
Speed	50 RPM
Media	[redacted]
Temperature	37.0°C ± 0.5°C
Sampling Time Points	15, 30 and 45 minutes
Number of Units	12
Method of Analysis	[redacted]
Specification	Q = [redacted] in 45 minutes [redacted] NLT [redacted] dissolved in 45 minutes for each active [redacted] if applicable

Table 11: Dissolution Results

	Mean Percent Dissolved (± SD) N = 12 (Time in Minutes)		
	Ibuprofen-Pseudoephedrine HCl - Chlorpheniramine maleate Clinical Trial Formulation (WH-0899-0005)		
Time (minutes)	Ibuprofen	Pseudoephedrine HCl	Chlorpheniramine maleate
15	97 ± 1.5	100 ± 1.9	101 ± 2.3
30	100 ± 1.5	101 ± 1.8	102 ± 1.8
45	99 ± 1.5	100 ± 1.7	101 ± 1.8

The applicant has proposed the dissolution condition (pH, apparatus, etc) without providing any justification for their choice. On a request from this reviewer, they replied

that final report on "Dissolution Method and Specification" will not be ready until August 26, 2002.

3. The applicant proposed a relatively wide dissolution specification (Q = —, in 45 minutes) without any documentation on the rationale for this choice. Review of the dissolution results suggest that a tighter specification of NLT —(—, where Q = — in 30 minutes as compared to the proposed— (Q) in 45 minutes would be appropriate for ensuring lot-to-lot uniformity of the drug product. This was based on the fact that > 99% of ibuprofen, pseudoephedrine HCl and chlorpheniramine was dissolved in 20 minutes. Therefore, it is recommended that dissolution specification be tightened to Q =— in 30 minutes.

4.6 Analytical

How were the active moieties identified and measured in plasma in the clinical pharmacology and biopharmaceutics studies?

For ibuprofen identification was by extraction of ibuprofen and an internal standard from human plasma. Analysis was by high performance liquid chromatography with ultraviolet detection. For pseudoephedrine identification was by extraction of pseudoephedrine and an internal standard from plasma. Analysis was by LC/MS/MS using —
For chlorpheniramine identification was by extraction of chlorpheniramine and an internal standard from plasma. Analysis was by — — detection.

Were the analytical methods used for the determination of ibuprofen and pseudoephedrine in biological fluids validated?

Yes, the method validation results demonstrate that the analytical method used for the quantitative determination of ibuprofen, pseudoephedrine and chlorpheniramine in human plasma were reliable and reproducible for the intended use. No endogenous peaks at the retention times of ibuprofen, pseudoephedrine and chlorpheniramine and the internal standard interfered with their quantitation. Ibuprofen, pseudoephedrine and chlorpheniramine were stable after 3 freeze-thaw cycles. Reproduced in the Table below are the analytical validation results for ibuprofen, pseudoephedrine and chlorpheniramine.

Table 12: Analytical Validation Results

Compound	Ibuprofen		Pseudoephedrine		Chlorpheniramine	
	AD99-01	AD99-03	AD99-01	AD99-03	AD99-01	AD99-03
Accuracy						
Precision (CV%)						
Standard curve range						
Sensitivity (LOQ)						

5. Detailed Labeling Recommendations

In light of the finding that in the fed treatment, mean *Tmax values were increased (≈ 1 hour) for pseudoephedrine and chlorpheniramine,* the applicant is suggested to address the effect of food on Tmax observed with *pseudoephedrine and chlorpheniramine* in Advil® Allergy Sinus Caplets in their proposed labeling.

2 pages redacted from this section of the approval package consisted of draft labeling

6.2 Individual Study Reviews

NDA: 21-441/Study AD-99-01 Study Date: Feb' 01 – Mar' 01

A Single-Dose, Randomized, Open-Label, Four-Way Crossover Pharmacokinetic Interaction Study Of Advil® Multi-Symptom Allergy Sinus

Objectives:

To compare the rate and extent of ibuprofen, pseudoephedrine, and chlorpheniramine absorption from to-be-marketed Advil Multi-Symptom Allergy Sinus (ibuprofen, pseudoephedrine hydrochloride, chlorpheniramine maleate) to currently marketed Nuprin® (ibuprofen), Sudafed Nasal Decongestant® (pseudoephedrine), and Chlor-Trimeton 4 Hour Allergy® (chlorpheniramine) under fasted conditions.

Study Design:

It was a single-center, randomized (stratified by gender), open-label, single-dose, four-way crossover pharmacokinetic interaction trial, with a 7-day washout period between the following treatments:

Treatment A: 2 x Advil® Multi-Symptom Allergy Sinus Caplets (ibuprofen 200 mg, pseudoephedrine hydrochloride 30 mg, chlorpheniramine maleate 2 mg per caplet, fasted)

Treatment B: 2 x Nuprin®Tablets (ibuprofen 200 mg per tablet, fasted)

Treatment C: 2 x Sudafed®Nasal Decongestant Tablets (pseudoephedrine hydrochloride 30 mg per tablet, fasted)

Treatment D: 1 x Chlor-Trimeton®4 Hour Allergy Tablet (chlorpheniramine maleate 4 mg per tablet, fasted)

Healthy male and female subjects received a single dose of one of the above four treatments during each study period under fasted conditions. Blood samples were collected pre-dose and at 15, 30, 45, 60, 75, and 90 minutes, and at 2, 3, 4, 6, 9, 12, 18, 24, 30, 36, 48, and 72 hours post-dose. Plasma samples were analyzed for racemic ibuprofen (up to 12 hours post-dose), pseudoephedrine (up to 36 hours post-dose), and/or chlorpheniramine (up to 72 hours post-dose) using specific, sensitive, and validated methodology.

AUCI (AUC from time 0 to infinity), AUCL (AUC from time 0 to the last measurable concentration), and Cmax, (both log-transformed and untransformed) were analyzed for

differences between treatments using an analysis of variance (ANOVA) model with effects for gender, subject nested within gender, period, treatment, and treatment-by-gender interaction. If the gender effect or the treatment-by-gender interaction was significant ($p \leq 0.10$), weight adjustment of the volume of distribution (Vd) and clearance (Cl) was performed and these parameters were analyzed using the same ANOVA model. If the effect/interaction was still apparent, AUCI, AUCL, Cmax, and their log-transformed counterparts were analyzed by gender group. Per FDA guidelines, a 90% two-sided confidence interval for the relative bioavailability of the treatments (test/reference), based on the least squares means (equivalent to two one-sided t-tests), was calculated for the following pairs of treatments:

- Treatment A vs. Treatment B*
- Treatment A vs. Treatment C*
- Treatment A vs. Chlor-Trimeton 4 Hour Allergy Tablets-fasted Treatment D*.

*Reference Product

For each of the above comparisons, bioequivalence was declared if the 90% two-sided confidence interval for the ratio (test/reference) was between 80% and 125% for log-transformed AUCI and Cmax or between 80% and 120% for the corresponding untransformed parameters.

Per protocol, at least 24 subjects were required to complete the study. A total of 29 subjects with the following demographics were enrolled and 28 completed all four treatment periods. Data from the 28 subjects that completed the study were included in the pharmacokinetic analyses; data from the 29 enrolled subjects (who received at least one dose of study medication) were included in the safety analyses.

Demographics: The average age, weight, and height of the population were 25.8 years (range: 18-42 years), 145.6 pounds (range: 109-180 pounds), and 67.6 inches (range: 62-77 inches), respectively. There were 14 males (48.3%) and 15 females (51.7%). The majority of subjects were Caucasian (58.6%), followed by Hispanic (27.6%), Black (6.9%), and Asian (6.9%).

Results:

Key pharmacokinetic parameters for ibuprofen, pseudoephedrine, and chlorpheniramine are summarized in Tables 1, 2, and 3 respectively. The corresponding mean plasma concentration versus time curves are shown in Figures 1, 2, and 3 respectively.

Table 1. AD-99-01 Key Ibuprofen PK Parameters: Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (mcg.h/mL)	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)	T½ (h)
Treatment A	112.01 (20.74)	114.00 (21.54)	32.71 (8.46)	1.84 (0.88)	1.89 (0.34)
Treatment B*	115.50 (23.40)	119.78 (24.28)	35.47 (8.51)	1.88 (1.16)	1.99 (0.37)
(A:B*)%^	97.04	94.79	92.00		
90%CI^	92.44-101.86	90.75-99.00	84.67-99.97		

A: Advil Multi-Symptom Allergy Sinus Caplets
B: Nuprin Tablets
*: Reference treatment
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

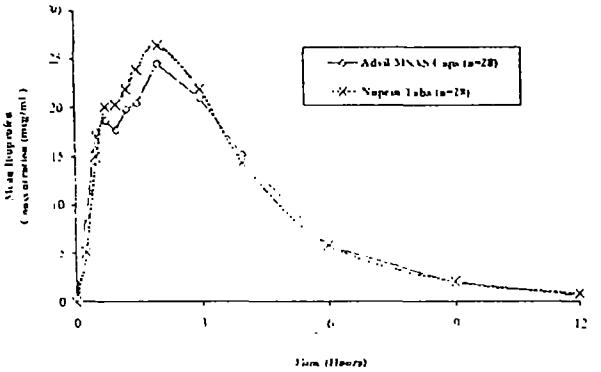


Figure 1: AD-99-01 Mean Ibuprofen Plasma Concentrations Over Time

Table 2. AD-99-01 Key Pseudoephedrine PK Parameters: Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Treatment A	1842.55 (374.00)	1870.14 (375.30)	236 04 (53.81)	1.69 (0.72)	4.84 (0.85)
Treatment C*	1769.50 (444.69)	1800.80 (450.53)	231.46 (57.90)	1.71 (0.73)	4.85 (0.94)
(A/C*)%^	106.28	105.98	103.08		
90%CI^	101.32-111.48	101.15-111.06	98.96-107.37		

A: Advil M ulti-Symptom Allergy Sinus Caplets
C: Sudafed Nasal Decongestant Tablets
*: Reference treatment
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

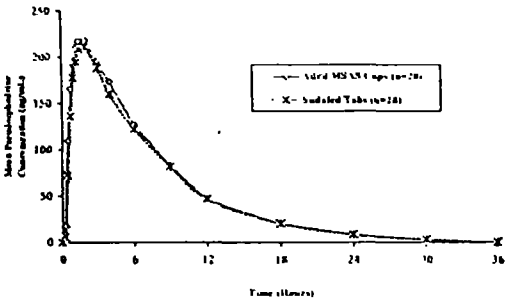


Figure 2: AD-99-01 Mean Pseudoephedrine Plasma Concentrations Over Time

Table 3. AD-99-01 Key Chlorpheniramine PK Parameters: Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Treatment A	150.31 (60.15)	179.86 (114.98)	7.79 (2.31)	3.10 (1.04)	21.06(15.90)
Treatment D*	140.73 (48.13)	162.47 (70.85)	7.27 (1.94)	3.40 (1.56)	20.58 (9.18)
(A/D*)%^	104.88	105.04	106.37		
90%CI^	99.06-111.05	98.84-111.62	101.13-111.88		

A: Advil Multi-Symptom Allergy Sinus Caplets
D: ChlorTrimeton 4 Hour Allergy Tablet
*: Reference treatment
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

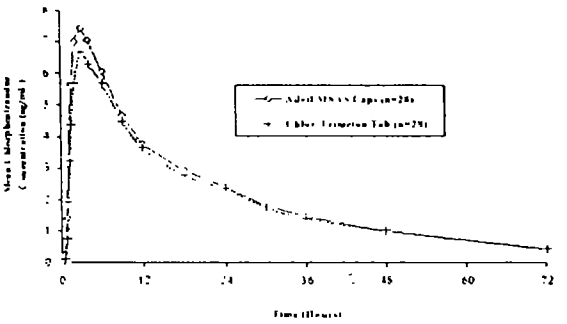


Figure 3: AD-99-01 Mean Chlorpheniramine Plasma Concentrations Over Time

Based on the ratio (test/reference) of the log-transformed mean Cmax and AUCI parameters, ibuprofen, pseudoephedrine, and chlorpheniramine in Advil Multi-Symptom Allergy Sinus Caplets were absorbed at the same rate and extent as the individual active ingredients in the reference treatments (ibuprofen in Nuprin, pseudoephedrine in Sudafed, and chlorpheniramine in Chlor-Trimeton), with 90% confidence intervals that fell within the acceptable bioequivalence range mentioned earlier. In addition, mean Tmax and $T_{½}$ values were also similar for ibuprofen, pseudoephedrine, and chlorpheniramine in Advil Multi-Symptom Allergy Sinus Caplets with the reference treatments.

For all three active ingredients, statistically significant ($p \leq 0.10$) gender effects and/or treatment-by-gender interactions were seen for several pharmacokinetic parameters. To examine if these effects/interactions were due to men generally weighing more than women, per protocol, Vd and Cl were adjusted for the subject's body weight and then analyzed statistically. Some of the gender effects and treatment-by-gender interactions remained significant after weight adjustment, suggesting that these effects/interactions were not due solely to weight differences between men and women. Therefore, the pharmacokinetic parameters were analyzed within each gender (summarized in Table 4).

Table 4. AD-99-01 Primary PK Parameters by Treatment and Gender: Mean (S.D.), Ratio, and 90% Confidence Interval (CI)

			AUCI (mcg.hr/mL)	Cmax (mcg/mL)
	Male	A: Mean (SD)	107.94 (23.48)	29.65 (8.85)
Ibuprofen				
		B: Mean (SD)	119.96 (30.34)	33.57 (10.97)
		(A/B*)% ^	90 05	89.94
		90% CI ^	85.16 – 95.22	76.92 – 105.17
	Female	A: Mean (SD)	119.26 (18.93)	35.36 (7.40)
		B. Mean (SD)	119.63 (19 28)	37.12 (5.50)
		(A/B*)% ^	99.74	94.23
		90% CI ^	93.06 – 106.89	86.42 – 102.75
			AUCI (ng.hr/mL)	**Cmax (ng/mL)**
	Male	A: Mean (SD)	1663.86 (234.60)	197.38 (28.45)
Pseudoephedrine				
		C Mean (SD)	1626 18 (430.63)	185.00 (14.47)
		(A/C*)% ^	107 03	106 59
		90% CI ^	100.81 – 113 63	98.83 – 114.96
	Female	A: Mean (SD)	2048.91 (388.22)	269.53 (47.96)
		C: Mean (SD)	1952.13 (423.85)	271.73 (50.44)
		(A/C*)% ^	105.98	99.70
		90% CI ^	99.17 – 113.27	94.40 – 105.30
			AUCI (ng.hr/mL)	**Cmax (ng/mL)**
	Male	A: Mean (SD)	144.53 (35 40)	6.92 (1.13)
Chlorpheniramine				
		D: Mean (SD)	149.48 (46.82)	6.48 (1.13)
		(A/D*)% ^	97.56	104.52
		90% CI ^	88.03 – 108.12	98.19 – 111.27
	Female	A: Mean (SD)	210.47 (149.19)	8.55 (2.81)
		D: Mean (SD)	173.73 (86.66)	7.95 (2.26)
		(A/D*)% ^	113.21	107.17
		90% CI ^	104.17 – 123.04	98.71 – 116.36

A: Advil M ulti-Symptom Allergy Sinus Caplets
B: Nuprin Tablets
C: Sudafed Nasal Decongestant Tablets
D: Chlor-Trimeton 4 Hour Allergy Tablets *: Reference treatment
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Within *females*, ibuprofen, pseudoephedrine, and chlorpheniramine were absorbed at the same rate and to the same extent (based on Cmax and AUCI) from Advil Multi-Symptom Allergy Sinus relative to the reference treatments, with confidence intervals that fell within the accepted bioequivalence limits. Within *males*, pseudoephedrine, and chlorpheniramine were absorbed at the same rate and to the same extent (based on Cmax and AUCI) from Advil Multi-Symptom Allergy Sinus relative to the reference treatments, with confidence intervals that fell within the accepted bioequivalence limits. However, for *ibuprofen*, the extent of absorption from Advil Multi-Symptom Allergy Sinus was same to the reference treatment, but the *rate of absorption* (based on Cmax)

was not same as 90% confidence limit was 76.92-105.17% which did not meet the accepted bioequivalence criteria. However, this difference was not clinically significant.

Discussion

This study compared the pharmacokinetics of ibuprofen, pseudoephedrine, and chlorpheniramine when administered in combination (Advil Multi-Symptom Allergy Sinus Caplets) and individually (Nuprin, Sudafed, and Chlor-Trimeton Tablets) to evaluate the potential for interaction effects. The combination of ibuprofen and pseudoephedrine has been available OTC from Whitehall-Robins Healthcare since 1989. Pharmacokinetic data on this combination product shows that are no interactions when these two ingredients are combined. Though the absence of pharmacokinetic interaction between ibuprofen and pseudoephedrine has been established, it was necessary to evaluate the potential for interaction effects when a third active ingredient (chlorpheniramine) was added to the combination.

The results from the present study showed that the pharmacokinetics of ibuprofen 400 mg, pseudoephedrine 60 mg, and chlorpheniramine 4 mg were not altered by co-administration as Advil Multi-Symptom Allergy Sinus Caplets. Based on Cmax and AUCI, the three active ingredients were absorbed at the same rate and to the same extent relative to each individual treatment. The pharmacokinetic parameters were also analyzed within each gender as statistically significant ($p \leq 0.10$) gender effects and/or treatment-by-gender interactions were seen for several pharmacokinetic parameters. The results showed that only for ibuprofen and within males only, Advil Multi-Symptom Allergy Sinus just missed bioequivalence in terms of rate of absorption (based on Cmax), with a 90% confidence limit of 76.92-105.17% compared to the reference. Though statistically significant, according to the sponsor, this result is not likely to be clinically meaningful. However, only clinical data can confirm that.

Conclusion

Though 90% confidence limit of Cmax for ibuprofen between Advil Multi-Symptom Allergy Sinus and reference Nuprin did not fall within accepted limit of 80 – 125% in males only , overall the pharmacokinetics of ibuprofen 400 mg, pseudoephedrine 60 mg, and chlorpheniramine 4 mg were not altered by co-administration as Advil Multi-Symptom Allergy Sinus Caplets. Based on Cmax and AUCI, the three active ingredients were absorbed at the same rate and to the same extent relative to each individual treatment (ibuprofen in Nuprin, pseudoephedrine in Sudafed, and chlorpheniramine in Chlor-Trimeton).

Comments:

The sponsor conducted a four-way crossover study to investigate the potential for a drug-drug interaction to occur. Under the regulations (21 CFR 320.25 (g)), this study should have been done as a two-way crossover with the test product compared to the concurrent administration of three separate singe entity products. Under this scenario if a drug-drug interaction occurred the sponsor would then do the more elaborate four way cross-over study to define the interaction. In doing this more definitive study instead of the "regulatory" study the sponsor was able to meet the required informational need and thus meet the intent of the regulations in a manner satisfactory to the Office of Clinical Pharmacology and Biopharmaceutics.

NDA: 21-441/Study AD-99-03 Study Date: Feb 2001

Advil® Multi-Symptom Allergy Sinus Food Effects Bioavailability Study

Objectives:

To characterize the rate and extent of absorption of ibuprofen, pseudoephedrine hydrochloride, and chlorpheniramine maleate from two Advil®Multi-Symptom Allergy Sinus caplets (ibuprofen 200 mg, pseudoephedrine hydrochloride 30 mg, and chlorpheniramine maleate 2 mg/caplet) when administered under fasted and fed conditions.

Study Design:

It was a single-center, randomized, open-label, single-dose, two-treatment, two-period, two-sequence crossover trial, with a washout period of 7 days between the treatments. Thirteen healthy subjects were enrolled to ensure that a minimum of 12 subjects (6 males and 6 females) completed the study. All enrolled subjects received a single oral dose of one of the two treatments described below during each of the two study periods.

Treatment A: Two Advil Multi-Symptom Allergy Sinus caplets (ibuprofen 200 mg, pseudoephedrine hydrochloride 30 mg, chlorpheniramine maleate 2 mg/caplet) - **fasted**

Treatment B: Two Advil Multi-Symptom Allergy Sinus caplets (ibuprofen 200 mg, pseudoephedrine hydrochloride 30 mg, chlorpheniramine maleate 2 mg/caplet) – **fed** (FDA recommended high fat breakfast: 2 eggs in butter, 2 pieces of bacon, 2 pieces of toast with butter, 4 ounces of hash brown, and 8 ounces of whole milk)

Healthy male and female subjects received a single dose of study medication under fed or fasted conditions during each period. Blood samples were drawn pre-dose, and at 15, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 9, 12, 18, 24, 30, 36, 48, and 72 hours post-dose. Plasma samples were assayed for racemic ibuprofen (HPLC), pseudoephedrine (LC/MS/MS), and/or chlorpheniramine —— using sensitive and validated methodology.

The area under the plasma concentration-time curve from time 0 to the last measurable concentration (AUCL), AUC from time 0 to infinity (AUCI), and peak plasma concentration (Cmax) were analyzed; time to Cmax (Tmax), half-life ($T_{½}$), elimination rate constant (Kel), volume of distribution (Vd), and clearance (Cl) were summarized. Descriptive statistics included (n, mean, SD, and CV%). AUC and Cmax parameters (both log-transformed and untransformed) were analyzed for differences between

treatments (fed versus fasted) using analysis of variance (ANOVA) with terms for gender, subject within gender, period, treatment, and treatment-by-gender interaction. If a significant gender or treatment-by-gender effect was found ($p \leq 0.10$), additional analyses adjusting for body weight were performed. If the gender or treatment-by-gender interaction was still present, subgroup analyses (by gender) were performed.AUCI and Cmax for the fed (test) and fasted (reference) treatments were analyzed for bioequivalence. Per Agency guidelines, bioequivalence was declared if the 90% CI of the ratio of the means (fed/fasted) of the log-transformed pharmacokinetic parameters fell within 80-125% for AUCI and 70-143% for Cmax.

Demographics: The subject population studied was 50% Caucasian, 50% Black. Similarly, 50% of the subjects were males and 50% females. The average age, weight, and height of the population were 30 years (range, 20-45 years), 163 pounds (range, 110-215 pounds), and 67 inches (range, 59-74 inches), respectively.

Results:

Key pharmacokinetic parameters for ibuprofen, pseudoephedrine, and chlorpheniramine under fed and fasted conditions are summarized in Tables 1, 2, and 3 respectively. Respective plasma concentrations over time are shown in Figures 1, 2, and 3. The results showed that the absorption of ibuprofen, pseudoephedrine, and chlorpheniramine from Advil Multi-Symptom Allergy Sinus caplets was not affected by the administration of food. However, in the fed treatment, mean Tmax values were increased (≈1 hour) for pseudoephedrine and chlorpheniramine.

Table 1: AD-99-03 Key Ibuprofen Pharmacokinetic Parameters (Mean ± SD and 90% CI

Treatment	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)
Fasted (A*)	128.39 (18.42)	32.25 (5.65)	1.73 (0.93)
Fed (B)	117.19 (23.76)	29.48 (9.72)	1.57 (0.84)
(B/A)% ^	90.41	88 64	
90% CI^	87.11-93.84	79.29-99.09	

*Reference formulation;
^ Based on the fitted log-transformed data

Figure 1: Mean Ibuprofen Plasma Concentrations (mcg/mL) Over Time (n = 12)

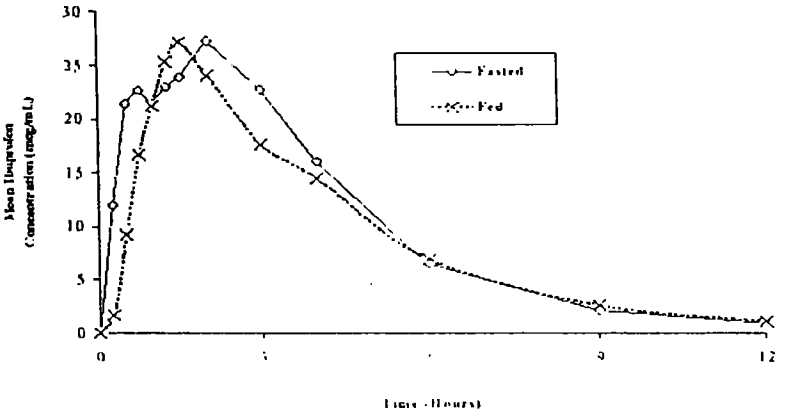


Table 2: Key Pseudoephedrine Pharmacokinetic Parameters (Mean SD and 90% CI)

Treatment	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)
Fasted (A*)	2065.89 (414.56)	223.75 (44.14)	1.52 (0.59)
Fed (B)	1997.17 (589.80)	206.25 (45.21)	2.80 (1.36)
(B/A)% ^	94.89	92.06	
90% CI^	88.73-101.47	84.34-100.48	

*Reference formulation;
^ Based on the fitted log-transformed data

Figure 2: Mean Pseudoephedrine Plasma Concentrations (ng/mL) Over Time (n = 12)

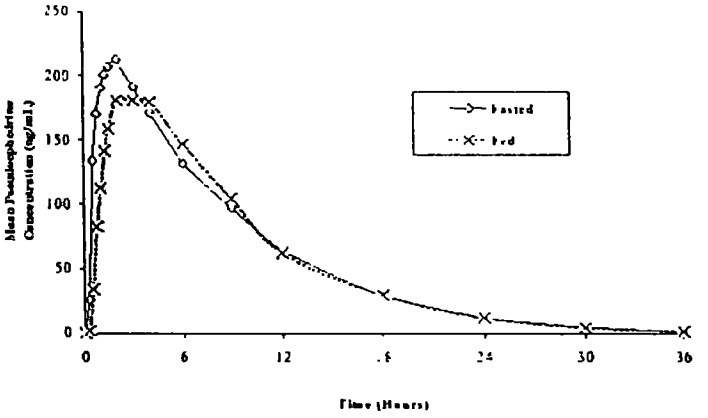
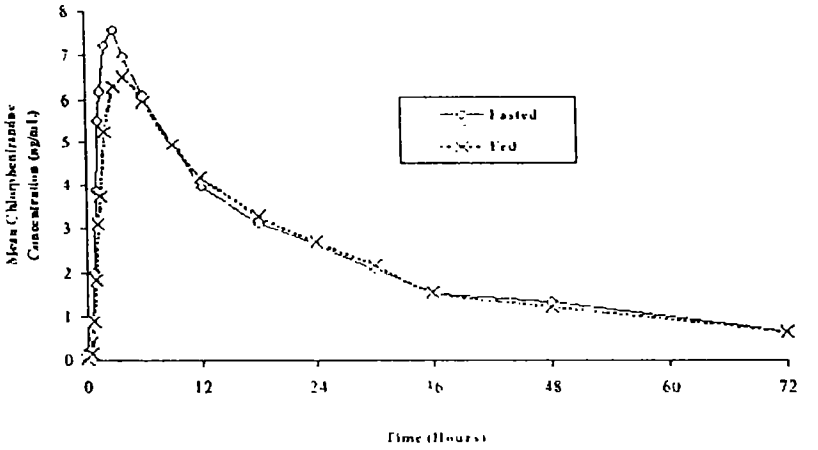


Table 3: Key Chlorpheniramine Pharmacokinetic Parameters (Mean ± SD and 90% CI)

Treatment	AUCI (ng·h/mL)	Cmax (ng/mL)	Tmax (h)
Fasted (A*)	202.55 (103.47)	8.00 (3.25)	2.88 (0.86)
Fed (B)	196.26 (88.77)	6.97 (1.93)	3.94 (1.95)
(B/A)% ^	98.94	89.56	
90% CI^	92.72-105.58	83.40-96.17	

*Reference formulation;
^ Based on the fitted log-transformed data

Figure 3: Mean Chlorpheniramine Plasma Concentrations (ng/mL) Over Time (n = 12)



In addition, a significant treatment-by-gender interaction ($p \leq 0.10$) for *pseudoephedrine* AUCI and C_{max} was observed in this study. The results obtained for the female subgroup were consistent with those of the entire population. The key findings for males and females are summarized in Table 4 and Table 5 respectively. However, despite the small sample size of this subgroup (n=6), both AUCI (CI = 77-100%) and C_{max} (CI = 75-110.8%) barely missed the accepted no food effect criteria of CI 80 – 125% for both. Again, this difference was not clinically significant.

Table 4: Pseudoephedrine Pharmacokinetic Parameters (Mean, SD, and 90% CI for Males Only (n=6)

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)	$T_{½}$ (h)
Fasted (A*)	1804.11 (221.12)	1834.01 (225 85)	199.17 (37.22)	1.33 (0.75)	5.44 (0.80)
Fed (B)	1584.06 (261.47)	1613.07 (257.56)	179.50 (21.38)	2.38 (0.97)	5.09 (0.70)
(B/A)% ^	87.37	87.59	91 01		
90% CI^	76.66-99.58	76.87-99.80	74.79-110.77		

* Reference formulation; ^: Based on the log-transformed parameters, the ratio of the antilog of the least-squares means are reported. Note: FDA Draft Guidance 'Food-Effect Bioavailability and Bioequivalence Studies' states t hat confidence i ntervals within 80%-125% for Ln AUCI and 70%-143% for Ln Cmax are indicative of no food effects

Table 5: Pseudoephedrine Pharmacokinetic Parameters (Mean, SD, and 90% CI for Females Only (n=6)

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)	$T_{½}$ (h)
Fasted (A*)	2267.24 (446.96)	2297.77 (445.02)	248.33 (38.08)	1.71 (0.33)	4.38 (0.41)
Fed (B)	2352.23 (595.51)	2381.27 (587.28)	233.00 (48.20)	3.22 (1.65)	4.37 (0.64)
(B/A)% ^	102.83	102 79	93.11		
90% CI^	92.96-113 75	93 24-113 32	85 97-100.84		

* Reference formulation, ^ Based on the log-transformed parameters, the ratio of the antilog of the least-squares means are reported Note FDA Draft Guidance 'Food-Effect Bioavailability and Bioequivalence Studies' states t hat confidence i ntervals within 80%-125% for Ln AUCI and 70%-143% for Ln Cmax are indicative of no food effects

Discussion

The present study was conducted to determine the effect of food on the bioavailability of ibuprofen, pseudoephedrine, and chlorpheniramine from the triple combination product. This study demonstrated that the rate and extent of absorption of ibuprofen, pseudoephedrine, and chlorpheniramine from Advil Multi-Symptom Allergy Sinus caplets were not different under fed and fasted conditions and mean Tmax values for pseudoephedrine and chlorpheniramine were increased under fed conditions. However, a significant treatment-by-gender interaction ($p \leq 0.10$), not explained by weight adjustment of Vd and Cl data, for pseudoephedrine AUCI and C_{max} was observed which according to the sponsor is likely not clinically meaningful although statistically significant. The formulation was found to be safe and well tolerated by healthy male and female subjects.

Conclusion

This study demonstrated that the rate and extent of absorption of ibuprofen, pseudoephedrine, and chlorpheniramine from Advil Multi-Symptom Allergy Sinus caplets were not different under fed and fasted conditions. However, mean Tmax values for pseudoephedrine and chlorpheniramine were increased under fed conditions. The formulation was found to be safe and well tolerated by healthy male and female subjects.

Office of Clinical Pharmacology and Biopharmaceutics (*New Drug Application Filing and Review Form)*

General Information About the Submission

	Information		Information
NDA Number	21-441	Brand Name	Advil Allergy Sinus
OCPB Division (I. II, III)	III	Generic Name	Ibuprofen 200 mg, Pseudoephedrine 30 mg and Chlorpheniramine 4 mg
Medical Division	HFD-550	Drug Class	Analgesic, nasal decongestant, antihistaminic
OCPB Reviewer	Tapash Ghosh	Indication(s)	
OCPB Team Leader	Dennis Bashaw	Dosage Form	Caplet
		Dosing Regimen	1 caplet every 4 to 6m hours
Date of Submission	March 1, 2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	August 1, 2002	Sponsor	Whitehall-Robins
PDUFA Due Date	June 1, 2003	Priority Classification	3S
Division Due Date	May 1, 2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2.				
Phase 3				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial.				
Population Analyses -				
Data rich.				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	1	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Is the in vivo bioavailability of the combination product equivalent to the in vivo bioavailability of each active ingredient administered as separate single ingredient preparations? What is the effect of food on the combination drug formulation? Is the observed "bioinequivalence' in rate of absorption of ibuprofen in males clinically relevant?	
Other comments or information not included above		
Primary reviewer Signature and Date	Tapash Ghosh (04/04/02)	
Secondary reviewer Signature and Date		

CC: NDA 21-441, HFD-850(Electronic Entry or Lee), HFD-550(J. Dean), HFD-880(Basaw, Selen, Lazor)

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

/s/

Tapash Ghosh
8/8/02 05:23:18 PM
BIOPHARMACEUTICS

Dennis Bashaw
8/9/02 05:51:36 PM
BIOPHARMACEUTICS