CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-587

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	**21-587**
Submission Date(s):	**04/23/03**
Brand Name:	**Children's Advil® Allergy Sinus/**
Generic Name:	**Ibuprofen/Pseudoephedrine/Chlorpheniramine Suspension(100mg/15mg/1 mg per 5 mL)**
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):	**Liquid Suspension, Ibuprofen (100mg), Pseudoephedrine HCl (15 mg) and Chlorpheniramine maleate (1 mg)/ 5 mL**
Indication:	**Relief of symptoms associated with allergic rhinitis and the common cold**

1 Executive Summary

In this application Wyeth is seeking approval for the liquid suspension dosage formulation containing a triple combination of ibuprofen (100 mg), pseudoephedrine (15 mg) and chlorpheniramine (1 mg) per 5 mL. The tablet/caplet dosage forms of the dual combination of ibuprofen and pseudoephedrine are currently marketed over-the-counter (OTC) as Advil Cold and Sinus tablets/caplet and Advil Flu and Body Ache caplets by the applicant. The first application for a triple combination of ibuprofen (IBU), pseudoephedrine (PSE) and chlorpheniramine (CHLOR) for adults and children of ages 12 years and older by the same applicant has been approved recently (NDA 21-441). This is the first application for the same triple combination in a suspension dosage form targeted for children of ages 6 to less than 12 years of age.

The sponsor conducted two biostudies in support of this application. The first study was a three way crossover bioavailability/food effect study with the proposed formulation using a recently approved caplet dosage form with the same composition as the reference standard. The second study was a bioavailability study with the proposed suspension formulation in children with allergy 6 to less than 12 years of age and comparison of the single dose pharmacokinetic profile with that obtained in healthy adults aged 18 to 45

years conducted in their previous NDA for caplet (NDA 21-441). With these two studies, the sponsor adequately described the pharmacokinetics of the three active ingredients, IBU, PSE and CHLOR following single dose administration of the triple combination suspension to healthy adults as well as allergic children aged 6 to less than 12 years of age. The systemic exposure data demonstrated that the rate and extent of absorption of IBU, PSE and CHLOR in the combination suspension: (1) was similar to that obtained from the combination caplet and (2) was similar between children (of age between 6 and less than 12 years) and adults (above 12 years old). The presence of food did not result in a significant change in the rate and exposure of IBU, PSE and CHLOR from the combination suspension except, food decreases the peak absorption (Cmax) of IBU which may not be clinically relevant.

1.1 Recommendation

Based on the data submitted in NDA 21-587, the application is acceptable from a clinical pharmacology and biopharmaceutics perspective provided the comments on dissolution specifications described in section 4.5 are adequately addressed.

Comments to be conveyed to the Applicant:

The sponsor claimed that their dissolution specifications conforms to USP acceptance criteria. However there is no approved suspension dosage form of the proposed combination and therefore there is no USP acceptance criteria *per se*.

Review of the dissolution results suggest that a tighter specification of [redacted](Q) in 10 minutes as compared to the proposed [redacted] in 10 minutes would be appropriate for ensuring lot-to-lot uniformity of the drug product. This was based on the fact that [redacted] of ibuprofen, pseudoephedrine HCl and chlorpheniramine was dissolved in 5 minutes. Therefore, it is recommended that dissolution specification be tightened to Q = [redacted] in 10 minutes.

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3 Summary of CPB Findings

Introduction and Background: The three active moieties in Advil® Allergy Sinus Suspension are IBU, PSE and CHLOR. IBU, 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. PSE hydrochloride is currently in the OTC final monograph for oral nasal decongestants for use in adults and children. CHLOR maleate is also currently in the OTC final monograph for oral antihistamines for use in adults and children. The proposed indication of the combination suspension is for temporary relief of symptoms associated with allergic rhinitis and the common cold.

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 100 mg ibuprofen, 15 mg pseudoephedrine, and 1 mg chlorpheniramine/5 ml for children of 6 to less than 12 years of age. 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 in the targeted children population.

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 vasoconstriction 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 did not conduct any **clinical study.** This NDA is supported by two pharmacokinetic studies (AR0002 and AR0003). 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 using
detection and analysis for chlorpheniramine was done using — chromatography with
All these methods were found to be reproducible and accurate and, therefore acceptable for the intended use.

Study AR0002 was conducted in healthy subjects to compare the rate and extent of absorption of IBU, PSE, and CHLOR from the proposed suspension to that of the recently approved caplet with the same composition. The study also evaluated food effect in the proposed suspension. The results demonstrate that for the suspension formulation, the rates (Cmax) and exposures (AUC) of IBU, PSE, and CHLOR are comparable to those from the caplet formulation (NDA 21- 441) under fasted condition except IBU in the triple combination suspension reached a greater Cmax in a shorter period of time (Tmax). Also, for the triple combination suspension formulation, the presence of food has no effect on the rates and exposures of IBU, PSE, or CHLOR except food decreases the peak absorption (Cmax) of IBU which may not be clinically relevant.

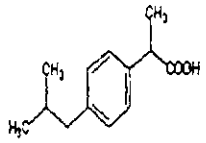
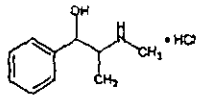
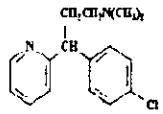
Study AR0003 was a single-dose pharmacokinetic study with the proposed Suspension in children 6 to less than12 years of age with symptoms of allergic rhinitis. The results indicated that the rates and exposures of IBU and PSE were comparable in children, relative to the corresponding values in healthy adults. However, for CHLOR the Cmax was similar for the two age groups, with an estimated difference of 14.4% between children and adults. The estimated exposure of CHLOR in the children was 26.7% less than adults. This lower AUC in children is likely due to their faster clearances (weight-adjusted), and is unlikely to be clinically meaningful because of previous experience with similar dose of CHLOR in approved dosage forms.

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 Suspension 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. Though the sponsor proposed to market [redacted] flavored (berry [redacted]) formulations, clinical pharmacology studies have been conducted using only berry flavored suspension (Ibuprofen 100 mg, Pseudoephedrine Hydrochloride 15 mg and Chlorpheniramine Maleate 1 mg) per 5 ml. However the minor difference is flavoring agents is not expected to make any difference in the outcome of the PK studies. The berry flavored formulation used in the PK studies is identical to the one of the proposed market formulation as outlined below. The proposed market formulation was utilized to manufacture the NDA batches.

Qualitative/Quantitative Composition (Berry flavored):

Component	%w/v (theoretical)	mg/5mL	Amount per Commercial Batch
Ibuprofen USP		100	
Pseudoephedrine HCl USP		15.0	
Chlorpheniramine Maleate USP		1.00	
Xanthan Gum NF			
Carboxymethyl Cellulose Sodium NF			
Polysorbate 80 NF			
Glycerin USP			
Sorbitol Solution USP			
Sodium Citrate USP/FCC			
Sodium Benzoate NF			
Edetate Disodium USP			
Citric Acid USP			
Flavor Artificial			
FD&C Red No. 40			
FD&C Blue No. 1			
Purified Water USP		L	

*Refer to

What is the proposed dosage and route of administration?

Children 48 – 95 lbs or 6 – 11 years of age, 2 teaspoons
Children under 48 lbs or 6 years, ask 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 rhinorrhea.

B. Therapeutic Indications:

The proposed indications for Advil® Allergy Sinus Suspension are for the temporary relief of the following symptoms associated with hay fever or other upper respiratory allergies, and sinusitis

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

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, IBU, PSE and CHLOR were appropriately identified and measured.

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

Reproduced in the Tables below are the pharmacokinetic parameters for ibuprofen obtained in Study AR 0002 (relative bioavailabilitystudy) and Study AR 0003 (Bioavailability study in children):

Table. 1. AR-00-02 Ibuprofen PK Parameters (Suspension-Fasted vs. Caplets-Fasted): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (mcg.h/mL)	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)	T½ (h)
Formulation A	119.04 (30.46)	122.44 (31.43)	40.52 (10.47)	0.78 (0.37)	2.39 (0.41)
Formulation C	125.06 (28.95)	129.71 (29.94)	30.89 (8.24)	1.88 (1.10)	2.36 (0.32)
(A/C*)%^	93.84	93.09	130.16		
90%CI^	87.94-100.13	87.11-99.98	118.08-143.48		

A: Suspension-Fasted; C: Caplets-Fasted; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 2. AR-00-02 Pseudoephedrine PK Parameters (Suspension - Fasted vs. Caplets - Fasted): 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	2048.36 (410.06)	2084.65 (418.18)	211.38 (35.50)	1.80 (0.59)	5.54 (1.08)
Formulation C	2102.83 (444.62)	2142.51 (455.38)	224.62 (39.51)	1.70 (0.68)	5.61 (1.10)
(A/C*)%^	97.53	97.43	94.02		
90%CI^	92.94-102.35	92.83-102.25	90.99-97.14		

A: Suspension-Fasted; C: Caplets-Fasted; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 3. AR-00-02 Chlorpheniramine PK Parameters (Suspension - Fasted vs. Caplets - Fasted): 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	170.77 (55.93)	193.50 (75.85)	7.95 (1.26)	3.23 (1.39)	21.55 (6.49)
Formulation C	176.79 (61.23)	203.08 (82.16)	8.05 (1.37)	3.22 (1.54)	21.97 (7.75)
(A/C*)%^	98.03	97.01	99.52		
90%CI^	92.03-104.43	90.18-104.36	94.49-104.82		

A: Suspension-Fasted; C: Caplets-Fasted; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 4. AR-00-03 Ibuprofen PK Parameters (Children vs. Adults): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (mcg.h/mL)	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)	T½ (h)
Adults (A)	119.04 (30.46)	122.44 (31.43)	40.52 (10.47)	0.78 (0.37)	2.39 (0.41)
Children (C)	112.73 (31.32)	114.79 (32.02)	36.58 (12.94)	1.14 (0.55)	1.83 (0.51)
(C/A)%^	92.82	92.06	87.69		
90%CI^	81.47-104.17	80.65-103.47	75.26-100.12		
p-Value (A vs C)	0.294	0.249	0.103		

A: Adults data from Study AR-00-02; C: Children data from Study AR-00-03

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 5. AR-00-03 Pseudoephedrine PK Parameters (Children vs. Adults): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Adults (A)	1961.24 (375.18)	2084.65 (418.18)	211.38 (35.50)	1.80 (0.59)	5.54 (1.08)
Children (C)	1699.24 (506.17)	1754.69 (515.37)	194.83 (46.91)	1.85 (0.65)	4.16 (0.62)
(C/A)%^	84.07	81.82	89.32		
90%CI^	74.21-93.42	72.45-91.19	81.75-96.88		
p-Value (A vs C)	0.006	0.002	0.022		

A: Adults data from Study AR-00-02; C: Children data from Study AR-00-03

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 6. AR-00-03 Chlorpheniramine PK Parameters (Children vs. Adults): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Adults (A)	151.96 (44.27)	193.50 (75.85)	7.95 (1.26)	3.23 (1.39)	21.55 (6.49)
Children (C)	113.90 (42.99)	130.92 (52.48)	7.34 (4.41)	2.89 (1.52)	13.96 (3.90)
(C/A)%^	73.50	66.54	89.23		
90%CI^	60.78-86.22	51.59-81.49	71.08-107.37		
p-Value (A vs C)	< 0.001	<0.001	0.325		

A: Adults data from Study AR-00-02; C: Children data from Study AR-00-03
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

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: Neither the gender effects nor treatment-by-gender interactions change the conclusions regarding bioequivalence.

Race: No statistical analysis using race as a covariate was performed by the sponsor.

4.4 Extrinsic Factors

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

Not adequately described.

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 IBU, PSE, and CHLOR under fed and fasted conditions are summarized in following Tables 7, 8, and 9 respectively. While food had no effect on the exposure of IBU, PSE and CHLOR, and on the rate of PSE and CHLOR, only for IBU, Cmax from the suspension under fed condition is below the lower bound bioequivalence limit of . However, the effect of food on the pharmacokinetics of IBU has been noted previously and should have no clinical effect. Previous studies evaluating the pharmacokinetic/ pharmacodynamic relationship between IBU plasma

concentration and analgesic effect indicate that plasma IBU concentrations of approximately 6 mcg/mL are associated with the onset of pain relief. In the present study, the mean plasma IBU concentration was greater than 6 mcg/mL at 15 minutes for both the fed (10.9 mcg/mL) and fasted (16.5 mcg/mL) states. Therefore no dosing adjustment recommendation may be warranted regarding administration of the product in relation to meals or meal types.

Table 7. AR-00-02 Ibuprofen PK Parameters (Suspension-Fasted vs. Suspension-Fed): 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	119.04 (30.46)	122.44 (31.43)	40.52 (10.47)	0.78 (0.37)	2.39 (0.41)
Treatment B	108.27 (22.69)	116.60 (28.67)	22.98 (4.77)	1.32 (0.95)	2.80 (0.82)
(B/A*)%^	90.87	94.66	56.95		
90%CI^	85.16-96.96	88.58-101.16	51.66-62.78		

A: Suspension-Fasted; B: Suspension-Fed; *: Reference Formulation ; ^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 8. AR-00-02 Pseudoephedrine PK Parameters (Suspension - Fasted vs. Suspension-Fed): 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	2048.36 (410.06)	2084.65 (418.18)	211.38 (35.50)	1.80 (0.59)	5.54 (1.08)
Treatment B	1968.08 (407.63)	1998.66 (409.60)	206.50 (33.76)	2.81 (1.00)	5.12 (1.12)
(B/A*)%^	95.63	95.48	97.40		
90%CI^	91.12-100.35	90.98-100.21	94.27-100.64		

A: Suspension-Fasted; B: Suspension-Fed; *: Reference Formulation
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Table 9. AR-00-02 Chlorpheniramine PK Parameters (Suspension - Fasted vs. Suspension - Fed): 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	170.77 (55.93)	193.50 (75.85)	7.95 (1.26)	3.23 (1.39)	21.55 (6.49)
Treatment B	171.82 (57.26)	196.06 (79.79)	7.48 (1.21)	3.56 (0.98)	21.62 (7.26)
(B/A*)%^	100.37	100.66	93.70		
90%CI^	94.22-106.92	93.57-108.29	88.97-98.69		

A: Suspension-Fasted; B: Suspension-Fed; *: Reference Formulation
^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

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

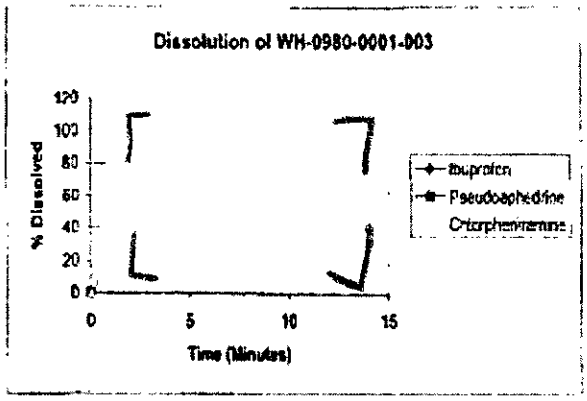
The proposed suspension formulation was developed under IND 63, 999. Clinical studies have been conducted using a suspension that is comparable to the proposed market formulation. Minor differences in manufacturing exist between the clinical supplies and the proposed formulation. However these differences were not sufficient to impact the chemical and dissolution data. The proposed dissolution method and results for the Advil Allergy Sinus suspension is reproduced in the Tables 10 and 11 and in the figure below:

Table 10: Dissolution Method and Specifications

Apparatus	USP Apparatus 2 Type- Paddles
Speed	50 RPM
Media	900 mL 50mM phosphate buffer, pH 6.5
Temperature	37.0°C
Sampling Time Points	5 and 10 minutes
Number of Units	12
Method of Analysis	HPLC
Specification	Not less than [redacted] in 10 minutes.

Table 11: Dissolution Results

	Mean Percent Dissolved (± SD) N = 12 (Time in Minutes)		
	Ibuprofen-Pseudoephedrine HCl - Chlorpheniramine maleate Clinical Trial Formulation (WH-0980-0001-003)		
Time (minutes)	Ibuprofen ± RSD	Pseudoephedrine HCl ± RSD	Chlorpheniramine maleate ± RSD
0	0	0	0
5	94 ± 1.3	98 ± 0.5	98 ± 0.5
10	97 ± 0.8	98 ± 0.5	98 ± 0



Based on the above results, the sponsor's proposed specifications are as follows:

Dissolution: Ibuprofen Pseudoephedrine HCl Chlorpheniramine maleate	Not less than [redacted] in 10 minutes. Conforms to USP acceptance criteria

The applicant claimed that their dissolution specifications conforms to USP acceptance criteria. However there is no approved suspension dosage from of the proposed combination and therefore there is no USP acceptance criteria *per se*.

Review of the dissolution results suggest that a tighter specification of NLT [redacted] in 10 minutes as compared to the proposed [redacted] in 10 minutes would be appropriate for ensuring lot-to-lot uniformity of the drug product. This was based on the fact that [redacted] of ibuprofen, pseudoephedrine HCl and chlorpheniramine was dissolved in 5 minutes. Therefore, it is recommended that dissolution specification be tightened to Q = [redacted] 10 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 [redacted]

For chlorpheniramine identification was by extraction of chlorpheniramine and an internal standard from plasma. Analysis was by gas chromatography [redacted]

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 [redacted] v 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	
	AR -0002	AD99-03	AR -0002	AD99-03	AR -0002	AD99-03
Accuracy						
Precision (CV%)						
Standard curve range						
Sensitivity (LOQ)						

5. Detailed Labeling Recommendations: None

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

6.2 Individual Study Reviews

NDA: 21-587/Study AR0002 Study Date: March 2' 02 – Mar 16' 02

A Three-Way Crossover Bioavailability/Food Effect Study of a Suspension Containing Ibuprofen (IBU) 100 mg, Pseudoephedrine Hydrochloride (PSE) 15 mg, and Chlorpheniramine Maleate (CHLOR) 1 mg/5mL

Objectives:

- To characterize the rate and extent of absorption of IBU, PSE, and CHLOR from a suspension containing IBU 100 mg, PSE 15 mg, and CHLOR 1 mg/5 mL when administered under fasted and fed conditions.
- To compare the rate and extent of absorption of IBU, PSE, and CHLOR from a suspension containing IBU 100 mg, PSE 15 mg, and CHLOR 1 mg/5 mL to a caplet containing IBU 200 mg/PSE 30 mg/CHLOR 2 mg under fasted conditions.

Study Design:

The study was designed as a single-center, randomized, open-label, single-dose, three-way crossover trial. Healthy male (14) and female (15) subjects received one of the following three treatments on three separate occasions, the order of which was randomly chosen. Each treatment was separated by no less than 14 days. During all 3 treatment periods, blood was drawn pre-dose (0) and at 15, 30, 45, 60, 75 and 90 minutes, and 2, 3, 4, 6, 9, 12, 24, 30, 36, 48, and 72 hours post-dose. Plasma levels of racemic IBU, PSE, and CHLOR were determined using specific, sensitive, and validated methodologies. All pharmacokinetic parameters were derived using WinNonlin® version 2.1) using the plasma concentrations and the sampling times provided by The statistical analyses were performed using SAS version 6.12

Treatment A. 20 mL of a suspension containing IBU 100 mg/PSE 15 mg/CHLOR 1 mg/5 mL (WH-0980-0001-003) under fasted conditions (total dose = IBU 400 mg/PSE 60 mg/CHLOR 4 mg)

Treatment B. 20 mL of a suspension containing IBU 100 mg/PSE 15 mg/CHLOR 1 mg/5 mL (WH-0980-0001-003) under fed conditions (total dose = IBU 400 mg/PSE 60 mg/CHLOR 4 mg)

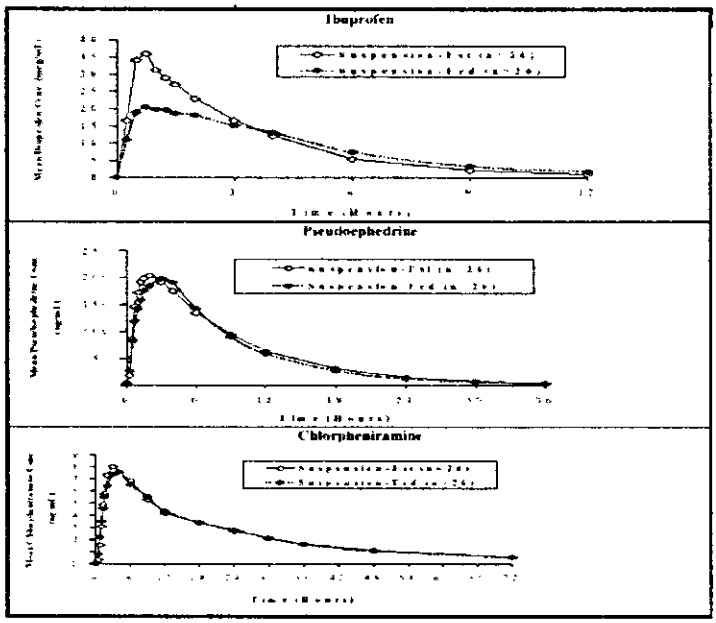
Treatment C. 2 x IBU 200 mg/PSE 30 mg/CHLOR 2 mg caplets (WH-0899-0005-002) under fasted conditions (total dose = IBU 400 mg/PSE 60 mg/CHLOR 4 mg).

For Treatment B, the following high fat breakfast was served within 30 minutes prior to dosing: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz. hash brown potatoes, and 8 oz. whole milk.

Results:

The mean plasma concentrations over time for the suspension-fasted versus the suspension-fed (food effect) are presented for IBU, PSE, and CHLOR in Figure S.1 (linear scale) and the mean plasma concentrations over time for the suspension-fasted versus caplets-fasted (formulation effect) are presented for IBU, PSE, and CHLOR in Figure S.2 (linear scale) respectively.

Figure S.1. AR-00-02 Mean Plasma Concentration Plots Over Time: Suspension-Fasted vs. Suspension-Fed



Ibuprofen Food Effect (Table S.1):. The 90% CI for Ln AUCL (area under the curve from time 0 to last measurable concentration) and Ln AUCI (area under the curve from time 0 to infinity) were within the accepted limits for bioequivalence. The 90% CI for Ln Cmax fell below the lower bound bioequivalence limit of —. Thus, the extent of IBU absorption from the suspension was equivalent under fed and fasted conditions but the rate of absorption was slower under fed conditions.

Table S.1. AR-00-02 Ibuprofen PK Parameters (Suspension-Fasted vs. Suspension-Fed): 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	119.04 (30.46)	122.44 (31.43)	40.52 (10.47)	0.78 (0.37)	2.39 (0.41)
Treatment B	108.27 (22.69)	116.60 (28.67)	22.98 (4.77)	1.32 (0.95)	2.80 (0.82)
(B/A*)%^	90.87	94.66	56.95		
90%CI^	85.16-96.96	88.58-101.16	51.66-62.78		

A: Suspension-Fasted; B: Suspension-Fed; *: Reference Formulation ; ^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Pseudoephedrine Food Effect (Table S.2). The 90% CI for Ln AUCI, Ln AUCL, and Ln Cmax were within the accepted limits for bioequivalence. Thus, the rate and extent of PSE absorption from the suspension were equivalent under fed and fasted conditions.

Table S.2. AR-00-02 Pseudoephedrine **PK Parameters (Suspension - Fasted vs. Suspension-Fed): 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	2048.36 (410.06)	2084.65 (418.18)	211.38 (35.50)	1.80 (0.59)	5.54 (1.08)
Treatment B	1968.08 (407.63)	1998.66 (409.60)	206.50 (33.76)	2.81 (1.00)	5.12 (1.12)
(B/A*)%^	95.63	95.48	97.40		
90%CI^	91.12-100.35	90.98-100.21	94.27-100.64		

A: Suspension-Fasted: B: Suspension-Fed; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Chlorpheniramine Food Effect (Table S.3). The 90% CI for L n AUCL, Ln AUCI, and Ln Cmax were within the accepted limits for bioequivalence. Thus, the rate and extent of CHLOR absorption from the suspension were equivalent under fed and fasted conditions.

Table S.3. AR-00-02 Chlorpheniramine **PK Parameters (Suspension - Fasted vs. Suspension - Fed): 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	170.77 (55.93)	193.50 (75.85)	7.95 (1.26)	3.23 (1.39)	21.55 (6.49)
Treatment B	171.82 (57.26)	196.06 (79.79)	7.48 (1.21)	3.56 (0.98)	21.62 (7.26)
(B/A*)%^	100.37	100.66	93.70		
90%CI^	94.22-106.92	93.57-108.29	88.97-98.69		

A: Suspension-Fasted; B: Suspension-Fed; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

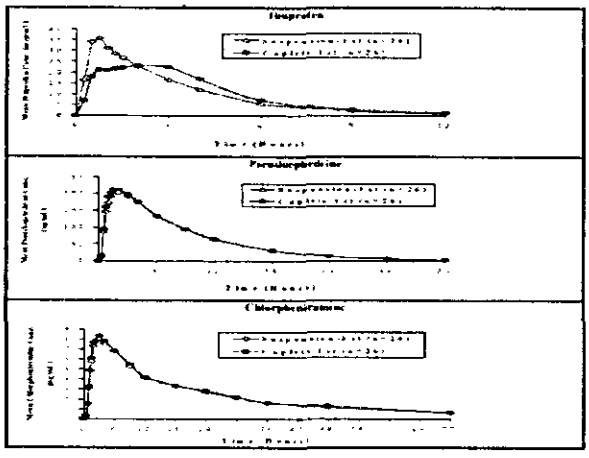


Figure S.2. AR-00-02 Mean Plasma Concentration Plots Over Time: Suspension-Fasted vs. Caplets-Fasted

Ibuprofen Formulation Effect (Table S.4). The 90% CI for Ln AUCL and Ln AUCI were within the accepted limits for bioequivalence. The upper bound of the 90% CI for Ln Cmax fell above the upper bound bioequivalence limit of . ——. Thus, the extent of IBU absorption from the suspension and caplet formulations was equivalent but the rate of absorption from the suspension was faster.

Table S.4. AR-00-02 Ibuprofen PK Parameters (Suspension-Fasted vs. Caplets-Fasted): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (mcg.h/mL)	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)	T½ (h)
Formulation A	119.04 (30.46)	122.44 (31.43)	40.52 (10.47)	0.78 (0.37)	2.39 (0.41)
Formulation C	125.06 (28.95)	129.71 (29.94)	30.89 (8.24)	1.88 (1.10)	2.36 (0.32)
(A/C*)%^	93.84	93.09	130.16		
90%CI^	87.94-100.13	87.11-99.98	118.08-143.48		

A: Suspension-Fasted; C: Caplets-Fasted; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Pseudoephedrine Formulation Effect (Table S.5). The 90% CI for Ln AUCL, Ln AUCI, and Ln Cmax were within the accepted limits for bioequivalence. Thus, rate and extent of PSE absorption from the suspension and caplet formulations were equivalent.

Table S.5. AR-00-02 Pseudoephedrine **PK Parameters (Suspension - Fasted vs. Caplets - Fasted): 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	2048.36 (410.06)	2084.65 (418.18)	211.38 (35.50)	1.80 (0.59)	5.54 (1.08)
Formulation C	2102.83 (444.62)	2142.51 (455.38)	224.62 (39.51)	1.70 (0.68)	5.61 (1.10)
(A/C*)%^	97.53	97.43	94.02		
90%CI^	92.94-102.35	92.83-102.25	90.99-97.14		

A: Suspension-Fasted; C: Caplets-Fasted; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Chlorpheniramine Formulation Effect (Table S.6). The 90% CI for Ln AUCL, Ln AUCI and Ln Cmax were within the accepted limits for bioequivalence. Thus, the rate and extent of CHLOR absorption from the suspension and caplet formulations were equivalent.

Table S.6. AR-00-02 Chlorpheniramine **PK Parameters (Suspension - Fasted vs. Caplets - Fasted): 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	170.77 (55.93)	193.50 (75.85)	7.95 (1.26)	3.23 (1.39)	21.55 (6.49)
Formulation C	176.79 (61.23)	203.08 (82.16)	8.05 (1.37)	3.22 (1.54)	21.97 (7.75)
(A/C*)%^	98.03	97.01	99.52		
90%CI^	92.03-104.43	90.18-104.36	94.49-104.82		

A: Suspension-Fasted; C: Caplets-Fasted; *: Reference Formulation

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Discussion

The purpose of this study was two-fold: to assess the effect of food on the rate and extent of absorption of IBU, PSE, and CHLOR from a combination suspension formulation and to evaluate the exposure to IBU, PSE, and CHLOR from the suspension formulation compared to a triple combination caplet formulation (NDA 21-441).

Food Effect: While food had no effect on the rate and exposure of PSE and CHLOR, for IBU, Cmax from the suspension under fed condition is below the lower bound bioequivalence limit of [redacted] However, the effect of food on the pharmacokinetics of IBU has been noted previously and should have no clinical effect. Previous studies evaluating the pharmacokinetic/ pharmacodynamic relationship between IBU plasma concentration and analgesic effect indicate that plasma IBU concentrations of approximately 6 mcg/mL are associated with the onset of pain relief. In the present study, the mean plasma IBU concentration was greater than 6 mcg/mL at 15 minutes for both the fed (10.9 mcg/mL) and fasted (16.5 mcg/mL) states.

Formulation Effect: For PSE and CHLOR, the AUC and Cmax for the suspension formulation were within the 90% CI for bioequivalence to the caplet formulation. However, for IBU, Cmax and Tmax for IBU in the triple combination suspension did not demonstrate bioequivalence to the triple combination caplet (Cmax: [redacted], respectively; upper bound of the 90% CI for Cmax (143.5%) fell above the upper bound bioequivalence limit of [redacted] Tmax: 0.78 hr vs. 1.88 hr, respectively). Nevertheless, the values obtained were well within the ranges found for Cmax and Tmax for single ingredient ibuprofen suspension in adults: Cmax ranged from [redacted] and Tmax ranged from 0.65 hr to 0.9 hr.

CONCLUSION:

Except for IBU which showed higher Cmax and shorter Tmax in the triple combination suspension, the overall comparable rate and exposure of the active ingredients from the suspension vs. the caplet (NDA 21- 441) supports a lack of interaction among the three ingredients in the suspension. Also, for the triple combination suspension formulation, the presence of food has no effect on the rate (Cmax) and exposure (AUC) of the active ingredients except that food decreases the rate of absorption of IBU.

NDA: 21-587/Study AR0003 Study Date: Jul 24 02 – Oct 14' 02

A Bioavailability Study of a Suspension Formulation of Ibuprofen/Pseudoephedrine Hydrochloride/Chlorpheniramine Maleate in Children 6 to <12 Years of Age with Symptoms Consistent with Allergic Rhinitis

Objectives:

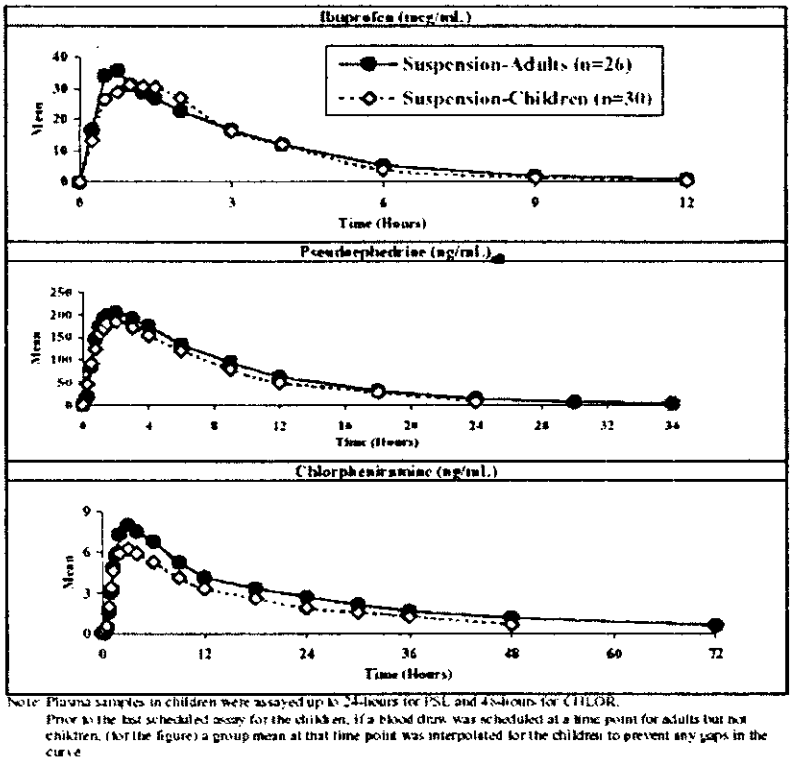
- To determine the maximum plasma concentration (C_{max}) and the area under the plasma concentration versus time curve (AUC) of ibuprofen (IBU), pseudoephedrine hydrochloride (PSE), and chlorpheniramine maleate (CHLOR) from a single 10-ml dose of Children's Advil Allergy Sinus Suspension (IBU 100 mg, PSE 15 mg, and CHLOR 1 mg/5 mL) in children 6 to <12 years of age with symptoms consistent with allergic rhinitis.

- To compare the single-dose pharmacokinetic profile of the triple combination suspension in allergic children aged 6 to <12 years to that obtained in healthy adults aged 18 to 45 years (Study AR-00-02).

Study Design: This was a multicenter, one-period, one-treatment, open-label, single-dose pharmacokinetic study of Children's Advil Allergy Sinus Suspension in children 6 to <12 years of age with symptoms of allergic rhinitis. Thirty-two subjects were planned and enrolled (13 males and 19 females) and 30 subjects completed the study. The two subjects that did not complete the study were excluded from all the pharmacokinetic analyses. Of the subjects enrolled, 13 (40.6%) were male and 19 (59.4%) were female. The average age, weight and height of the subject sample was 9.0 years (range, 6 to 11 years), 75.5 lbs. (range, 38 to 120 lbs.), and 53.8 inches (range, 44 to 61 inches), respectively. The majority of the subjects were Caucasian (53.1%), followed by Black (31.3%), Hispanic (12.5%), and Other (3.1%). Eligible subjects received a single 10-mL oral dose of Children's Advil Allergy Sinus Suspension (WHR-0980-0001-003) via a disposable dosing syringe, followed by 20 mL of water. Blood samples (approximately 2.5 mL) were collected prior to (up to 4 hours prior to dosing) and at 0.5, 1, 1.5, 2, 3, 6, 9, 12, 24 and 48 hours after dosing. The total volume of blood drawn from each subject was approximately 29.5 mL. Plasma levels of racemic IBU, PSE, and CHLOR were determined using specific, sensitive, and validated methodologies described in detail in Study 002.

Results: All pharmacokinetic parameters were derived using WinNonlin® version 2.1 [redacted] using the plasma concentrations and the sampling times provided by [redacted] The statistical analyses were performed using SAS version 6.12 [redacted]

The mean plasma concentration over time for IBU, PSE and CHLOR are shown in Figure S.1. The results of the pharmacokinetic comparison in children versus adults are summarized in Table S.1 for IBU, Table S.2 for PSE, and Table S.3 for CHLOR.



Note: Plasma samples in children were assayed up to 24-hours for PSE and 48-hours for CHLOR. Prior to the last scheduled assay for the children, if a blood draw was scheduled at a time point for adults but not children, (for the figure) a group mean at that time point was interpolated for the children to prevent any gaps in the curve

Figure S.1. AR-00-03 Mean Plasma Concentration Plots Over Time (Linear Scale)

Ibuprofen: The 90% CI for Ln AUCL and Ln AUCI were within the accepted limits for bioequivalence between adults aged 18 to 45 years and children aged 6 to <12 years population. However, the lower bound of the 90% CI for Ln Cmax fell below the lower bound bioequivalence limit of — Thus, the extent of IBU absorption from the suspension between two populations was equivalent but the rate of absorption in the children population was slower.

Table S.1. AR-00-03 Ibuprofen PK Parameters (Children vs. Adults): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (mcg.h/mL)	AUCI (mcg.h/mL)	Cmax (mcg/mL)	Tmax (h)	T½ (h)
Adults (A)	119.04 (30.46)	122.44 (31.43)	40.52 (10.47)	0.78 (0.37)	2.39 (0.41)
Children (C)	112.73 (31.32)	114.79 (32.02)	36.58 (12.94)	1.14 (0.55)	1.83 (0.51)
(C/A)%^	92.82	92.06	87.69		
90%CI^	81.47-104.17	80.65-103.47	75.26-100.12		
p-Value (A vs C)	0.294	0.249	0.103		

A: Adults data from Study AR-00-02; C: Children data from Study AR-00-03

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Pseudoephedrine: The lower bound of the 90% CI for Ln AUCL, Ln AUCI fell below the lower bound bioequivalence limit of — . The 90% CI for Ln Cmax were within the accepted limits for bioequivalence. Thus, the rate of PSE absorption between the two populations was equivalent but the extent of PSE absorption was somewhat lower in children compared to adults.

Table S.2. AR-00-03 Pseudoephedrine PK Parameters (Children vs. Adults): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Adults (A)	1961.24 (375.18)	2084.65 (418.18)	211.38 (35.50)	1.80 (0.59)	5.54 (1.08)
Children (C)	1699.24 (506.17)	1754.69 (515.37)	194.83 (46.91)	1.85 (0.65)	4.16 (0.62)
(C/A)%^	84.07	81.82	89.32		
90%CI^	74.21-93.42	72.45-91.19	81.75-96.88		
p-Value (A vs C)	0.006	0.002	0.022		

A: Adults data from Study AR-00-02; C: Children data from Study AR-00-03

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Chlorpheniramine: The lower bound of the 90% CI for Ln AUCL, Ln AUCI and Ln Cmax fell below the lower bound bioequivalence limit of — demonstration slower rate and lesser extent of absorption of CHLOR in children population compared to adult population. The estimated total exposure (AUC48) for the children was 26.7% lower. The reduced AUC seen in children is likely due to a faster clearance (Cl) of CHLOR, supported by a shorter terminal elimination half-life ($t_{½}$) in children (14 hours) versus adults (22 hours) observed in previous cases. The corresponding Cl values for children and adults were 0.52 and 0.33 L/hr/kg.

Table S.3. AR-00-03 Chlorpheniramine PK Parameters (Children vs. Adults): Mean (S.D.) and 90% Confidence Interval (CI)

	AUCL (ng.h/mL)	AUCI (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	T½ (h)
Adults (A)	151.96 (44.27)	193.50 (75.85)	7.95 (1.26)	3.23 (1.39)	21.55 (6.49)
Children (C)	113.90 (42.99)	130.92 (52.48)	7.34 (4.41)	2.89 (1.52)	13.96 (3.90)
(C/A)%^	73.50	66.54	89.23		
90%CI^	60.78-86.22	51.59-81.49	71.08-107.37		
p-Value (A vs C)	< 0.001	<0.001	0.325		

A: Adults data from Study AR-00-02; C: Children data from Study AR-00-03

^: Based on the log-transformed parameters; the ratio of the antilog of the least-squares means is reported.

Discussion: It should be noted that the 90% confidence intervals included in the Tables above required a cross-study comparison. The purpose of study AR-00-03 is to compare the total systemic exposure, (AUC) and the peak exposure, (Cmax) of IBU, PSE and CHLOR from the combination suspension when administered to children versus the systemic exposure obtained for the suspension in healthy adults in Study AR-00-02. Notably, for chlorpheniramine, AUC confidence intervals are somewhat lower, 62% for AUCL (48 hours) and 56% for AUCI. This reduced AUC in children is likely due to their faster clearances (weight- adjusted), and is unlikely to be clinically meaningful based on previous experience. Given the fact that for chlorpheniramine maleate and pseudoephedrine hydrochloride, the sponsor's proposed dose in the pediatric population (6 – under 12 years of age) is within the dose specified in OTC monograph, strict adherence to bioequivalence criteria between the two populations may not be critical. For ibuprofen, though C_{max} is little below the acceptable lower limit of confidence interval of the ratio between the two, this minor difference should not affect efficacy.

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

General Information About the Submission

	Information		Information
NDA Number	21-587	Brand Name	Advil Allergy Sinus Suspension
OCPB Division (I, II, III)	III	Generic Name	Ibuprofen 100 mg, Pseudoephedrine 15 mg and Chlorpheniramine 1 mg/ 5 mL
Medical Division	HFD-550	Drug Class	Analgesic, nasal decongestant, antihistaminic
OCPB Reviewer	Tapash Ghosh	Indication(s)	Temporary relief of symptoms associated with hay fever or other upper respiratory tract allergies
OCPB Team Leader	Dennis Bashaw	Dosage Form	Suspension
		Dosing Regimen	2 tsp every 4 to 6m hours
Date of Submission	April 23, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review	November 15, 2003	Sponsor	Whitehall-Robins
PDUFA Due Date	February 24, 2004	Priority Classification	3S
Division Due Date	November 7, 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.	X			
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-	[redacted]	[redacted]		
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 suspension product equivalent to the in vivo bioavailability of combination caplet? What is the effect of food on the combination suspension formulation ? Is the in vivo bioavailability of the combination suspension product similar in adult and children population?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Tapash Ghosh (05/28/03)**	
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
12/24/03 12:55:41 PM
BIOPHARMACEUTICS

Dennis Bashaw
12/24/03 02:54:21 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL