CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-374

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	**21-374**	**Submission Date(s): 07/24/01**
Brand Name:		**Advil® Cold and Sinus Liquigels®**
Generic Name:		**Ibuprofen/Pseudoephedrine (200mg/30mg)**
Reviewer:		**Abimbola Adebowale Ph.D.**
Team Leader:		**Dennis Bashaw Pharm.D.**
OCPB Division:		**DPEIII**
ORM division:		**HFD-550**
Sponsor:		**Wyeth Consumer Healthcare, Madison, NJ**
Relevant IND(s):		
Submission Type; Code:		**3S**
Formulation; Strength(s):		**Liquigel Capsule, Ibuprofen (200mg) and Pseudoephedrine HCl (30 mg)**
Indication:		**Pain Reliever/Fever Reducer/Nasal Decongestant**

1 Executive Summary

In this application the sponsor is seeking approval for the liquigel dosage formulation of a combination of ibuprofen (200 mg) and pseudoephedrine (30 mg). The tablet/caplet dosage form of the combination, Advil Cold and Sinus tablets/caplet, (NDA 19-771 approved in 1989) is currently marketed over-the-counter (OTC) by the applicant. The applicant included two pharmacokinetic studies (AB-00-04 and AB-00-05) in this NDA. Study AB-00-04 characterized the rate and extent of absorption of ibuprofen and pseudoephedrine from the combination liquigel in healthy adults. Study AB-00-05 was a single dose food effects study of the combination liquigel.

1.1 Recommendation

Based on the data submitted in NDA 21-374, the applicant has met the requirements outlined in 21 CFR 320 and their application is acceptable from a clinical pharmacology and biopharmaceutics perspective provided, the labeling recommendations and the dissolution methodology and specifications described in section 4.5 and 5 are adequately addressed.

The applicant adequately described the pharmacokinetics of the two active ingredients, ibuprofen and pseudoephedrine following single dose administration of the combination liquigel product to healthy adults. The systemic exposure data demonstrated that the extent of absorption of ibuprofen and pseudoephedrine in the combination liquigel product was similar to that of the individual components administered separately. The rate of absorption of ibuprofen and pseudoephedrine was not similar to that of the

individual components. For the combination liquigel and tablet formulation, the rate and extent of absorption of pseudoephedrine was bioequivalent from both formulations. However, for ibuprofen, only the extent of absorption for both formulations was similar, the rate was not.

Although the rate of absorption obtained for ibuprofen from the combination liquigel was not similar to that of the individual component and the combination tablet, it was between that of the two already approved products. Therefore, the difference in the rate of absorption is unlikely to be clinically significant in terms of efficacy. The rate of absorption obtained with the combination liquigel for pseudoephedrine was higher than that obtained with the single ingredient product but similar to that of the combination tablet. Following discussions with the medical reviewer I was informed that the global safety data for the combination tablet was not different from that for the single ingredient tablet. Therefore, it is unlikely that the related incidence rates for adverse experiences will be higher for the liquigel. Based on the aforementioned, the data indicated that the rate and extent of absorption of either ibuprofen or pseudoephedrine hydrochloride was not clinically affected by the presence of the other when administered as a combination liquigel to adults.

The presence of food resulted in a decrease in the rate of absorption of ibuprofen from the combination liquigel, however no food effect was demonstrated for pseudoephedrine. The applicant addressed this food effect in their proposed label by including the phrase ——— and "Take with food or milk if stomach upset occurs". Although the data indicates a 15-30 minute delay in the onset of pain relief due to the presence of food, the increased possibility of GI toxicity when NSAID's are administered on an empty stomach was more of a clinical concern. If a patient does experience stomach upset, it may be more appropriate to discontinue the use of the medication and also food or milk may not always provide relief if stomach upset occurs. Therefore the clinical division (HFD-560) decided that it would be better if the applicant modified their proposed label by———

Comments to be conveyed to the Applicant:

1. In the proposed dissolution method the applicant had a ——— speed of ——— without any documentation on the rationale for this choice. Following discussions with the chemistry reviewer it was decided that the applicant would need to provide a scientific rationale and, adequate data at lower agitation speeds to support their choice given the liquid gel nature of the product.
2. In future submissions the applicant should provide detailed information on the sample clean up process and the purity and identity of the internal standard used in the assay development report.

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3 Summary of CPB Findings

Introduction and Background: The two active moieties in Advil® Cold and Sinus liquigel are ibuprofen and pseudoephedrine. 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. The proposed indication of the combination liquigel is for use in temporarily relieving the symptoms associated with cold, sinusitis, or flu.

Clinical Pharmacology: This NDA is supported by two pharmacokinetic studies (AB-00-04 and AB-00-05). The applicant also provided supporting literature on the pharmacokinetics and pharmacodynamics of ibuprofen and pseudoephedrine in children. Study AB-00-04 characterized the rate and extent of absorption of ibuprofen and pseudoephedrine from the combination liquigel in healthy adults. The treatments evaluated were Advil® Cold & Sinus liquigel (ibuprofen 200 mg/pseudoephedrine HCl 30 mg), Advil® liquigel (Ibuprofen 200mg) and Children's Sudafed Nasal Decongestant Liquid Medication (pseudoephedrine HCl 15 mg/5 mL) and Advil Cold & Sinus Tablet (ibuprofen 200 mg/pseudoephedrine HCl 30 mg). The results of this study demonstrated that the extent of absorption of ibuprofen and pseudoephedrine HCl from the combination liquigel were similar to those obtained for the individual components and the combination tablet. The rate of absorption of ibuprofen and pseudoephedrine were not similar to that of the individual components and that of ibuprofen was not similar to that of the combination tablet. The rate of absorption for pseudoephedrine was similar to that of the combination tablet. Therefore the data suggests that the rate of absorption of either component was affected by the presence of the other when administered as the combination liquigel to adults. However, based on the literature reports of the PK/PD of ibuprofen and the global safety reports, these interactions were not considered to be clinically relevant.

Biopharmaceutics: Study AB-00-05 was a single dose food effects study of the combination liquigel. The results indicated that food decreases the rate of absorption of ibuprofen but not the extent. No food effect was observed for pseudoephedrine from a combination liquigel formulation.

For the dissolution method proposed by the applicant the agitation speed value was [redacted] This speed appears [redacted] for maximum discriminating power and, to detect products with poor in vivo performance. Therefore, the applicant would need to provide adequate information to justify the choice of this speed. Also a preliminary review of the dissolution results suggest that a tighter specification of NLT [redacted] (Q) instead of the proposed [redacted] (Q) in 30 minutes, would be appropriate for ensuring lot-to-lot uniformity of the drug product. This was based on the fact that [redacted] of ibuprofen and pseudoephedrine HCl was dissolved in [redacted] minutes.

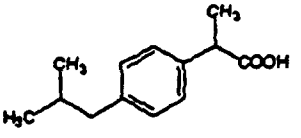
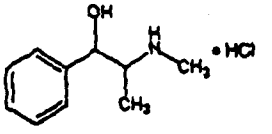
In the pharmacokinetic studies, analysis for ibuprofen was by [redacted] and for pseudoephedrine it was [redacted] Both methods were found to be reproducible and accurate and, therefore acceptable for the intended use.

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 Cold and Sinus Liquigels are as follows:

Drug Name	Ibuprofen	Pseudoephedrine hydrochloride
Chemical Name	(±)-2-(p-isobutylphenyl) propionic acid	Benzenemethanol, α-[1 (methylamino) ethyl]-,[S-(R*, R*)]-,hydrochloride
Structure		
Molecular formula	$C_{13}H_{18}O_2$	$C_{10}H_{15}NO.HCl$
Molecular weight	206.29	201.70
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
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
Solubility	Low solubility in water, Soluble in alcohol, acetone and chloroform. Soluble in an aqueous solution of alkali hydroxides and carbonates.	Soluble in water (1 g in 0.5 mL water), 3.6 mL alcohol, 91 mL chloroform, 7000 mL ether

B. The proposed to-be-marketed formulation of Advil® Cold Sinus liquigel contains 200 mg ibuprofen and 30mg pseudoephedrine HCl. The inactive ingredients are as follows: Gelatin, NF, FD&C red no. 40, D & C yellow No. 10, ink, polyethylene glycol NF, potassium hydroxide, NF and, purified water, USP. (A copy of the Qualitative/Quantitative composition statement is attached in the Appendix in Section 6.2.4 on page 27). The formulation used in the clinical studies (Batch No. WH-0686-0008-002) was the same as the proposed-to-be-marketed formulation.

What is the proposed dosage and route of administration?

One capsule every 4-6 hours while symptoms persist. If symptoms do not respond to 1 capsule, 2 capsules may be used. Do not use more than 6 capsules in any 24-hour period unless directed by 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.

[redacted]

Pseudoephedrine is a s
Pseudoephedrine acts directly c
receptors. By acting directly
respiratory tract, pseudoephedri
nasal mucous membranes, reduc
increases nasal airway patency.

B. Therapeutic Indications:

The proposed indications for Adv
of the following symptoms asso
congestion, headache, body aches

4.2 General Clinical Pharmacolo

Were the active moieties in the pla
and measured to assess pharmacoki

Yes, the active moieties,
identified and measured (refer to th

What are the pharmacokinetic par
Cold and Sinus Liquigel?

Reproduced in the Table below
obtained in Study AB-00-04 (relativ
effects study)

**Table 1. Pharmacokinetic par
Cold and Sinus Liquigel in healthy**

Study #.	
N	
Age Range (years)	
Weight Range (pounds)	
Single Dose (mg)	
Cmax (µg/ml)	
AUC_{inf} (µg.h/ml)	1
AUC_{0-24}(µg.h/ml)	1
Tmax (h)	
Cl/F (L/h)	
Vd/F (L)	1
$T_{1/2}$ (h)	
Kel (1/h)	0

[redacted]

Table 2. Pharmacokinetic parameters [Mean (CV%)] of Pseudoephedrine from Advil Cold and Sinus Liquigel in healthy adults in the fasted state

Study #.	AB-00-04	AB-00-05
N	27	25
Age Range (years)	20-44	18-44
Weight Range (pounds)	108-225	110-192
Single Dose (mg)	60	60
Cmax (ng/ml)	219.04 (36.11)	254.40 (21.26)
AUC_{inf} (ng.h/ml)	2134.90 (35.09)	2424.16 (25.87)
AUC_{0-24} (ng.h/ml)	2023.49 (32.03)	2289.38 (22.76)
Tmax (h)	2.40 (50.43)	2.06 (38.23)
Cl/F (L/h)	30.67 (26.40)	26.30 (24.26)
Vd/F (L)	217.10 (26.07)	187.86 (18.86)
$T_{1/2}$ (h)	5.03 (20.04)	5.14 (24.27)
Kel (1/h)	0.14 (18.71)	0.14 (20.21)

The mean PK parameters obtained for ibuprofen and pseudoephedrine between studies are similar for the 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?

The intra-subject and inter-subject variability expressed as the CV % variability for the healthy adult subjects following the administration of Advil Cold and Sinus Liqui-gels are reproduced in Table 3 below:

Table 3: Inter-subject and Intra-subject Variability of Ibuprofen and Pseudoephedrine from the Combination Liqui-gel

Type of Variability/PK Parameters	AB-00-04 (CV%)		AB-00-05 (CV%)	
Intra-subject	Ibuprofen	Pseudoephedrine	Ibuprofen	Pseudoephedrine
AUC inf	9.72	12.15	10.06	10.39
AUC t	9.89	12.09	9.86	9.95
Cmax	25.79	16.09	28.86	14.71
Inter-subject				
AUC inf	24.83	35.09	22.11	25.87
AUC t	25.42	32.03	21.48	22.76
Cmax	38.71	36.11	25.36	21.26
Tmax	40.88	36.11	77.31	38.23
CL/F	23.52	26.40	27.32	24.26
Vd/F	92.11	26.07	29.37	18.86
T1/2	26.36	20.04	39.95	24.27

The intra-subject variability of AUC and Cmax were less than 30% for both ibuprofen and pseudoephedrine in the healthy adults. The intra-subject variability associated with ibuprofen's Cmax appeared relatively high (>20%) for both studies. The inter-subject variability of the PK parameters ranged between 18.86 - 39.95% for most of the parameters except Tmax (36.11-77.31%) and, Vd/F for ibuprofen (92.11%) in study # AB-00-04 which was 3 fold higher than that obtained in AB-00-05. Low values of Kel from two patients (#'s 107 and 117) probably also contributed to this variability obtained with the Vd.

4.3 Intrinsic Factors

What intrinsic factors influence exposure?

Gender: In the statistical analysis the gender and treatment by gender effect was tested (significance was defined as $p \leq 0.10$). A significant gender effect ($p < 0.053$) for AUC_{inf}, AUC_{last} and C_{max} was obtained for ibuprofen and pseudoephedrine in study # AB-00-04 (19 males and 8 females completed). An evaluation of the Vd and Cl adjusted for subject's body weight demonstrated that the gender effect was significant ($p = 0.067$) for the adjusted Cl of ibuprofen. This suggested that the gender differences for ibuprofen were not only due to men generally weighing more than women. The results of further analysis of the pharmacokinetic parameters is reproduced in Table 4 below:

Table 4. Comparison of the Pharmacokinetic Parameters (Mean [CV%]) of Ibuprofen from Advil Cold and Sinus Liquigel between Male and Female Adults

Gender	Male	Female
N	19	8
Single Dose (mg)	400	400
AUC_{0-24}(mcg.h/ml)	99.25 (26.44)	123.62 (17.57)
AUC_{inf} (mcg.h/ml)	102.81 (25.75)	123.67 (18.92)
Cmax (mcg /ml)	29.57 (36.54)	48.83 (19.87)
Tmax (h)	1.24 (84.82)	0.76 (14.86)
$T_{1/2}$ (h)	3.26 (84.15)	3.30 (58.53)
Kel (1/h)	0.28 (36.72)	0.26 (42.52)
Cl/F (L/h)	4.11 (22.58)	3.34 (19.25)
Vd/F (L)	19.54 (99.04)	15.46 (51.91)

The data in Table 4 above shows that the extent of absorption was about 19% higher and the Cmax was about 39% higher in females than in males. Also the males had a higher clearance (~18%) than the females. The applicant stated that the gender effect seen in study AB-00-04 may be attributable to the small number of females that participated in that study compared to those in study #AB-00-05. This could also be indicative of a possible gender-based subject by formulation interaction. However, in

study # AB-00-05 (13 males and 12 females completed) there was no gender effect observed with ibuprofen.

Although a significant gender effect for AUC_{last} and C_{max} was found for pseudoephedrine ($p < 0.059$) in Study AB-00-05, following weight normalization of Vd and Cl, this was not statistically significant ($p > 0.64$). This suggested that the observed gender differences were probably due to men generally weighing more than women. This was also consistent with the results obtained for pseudoephedrine in study # AB-00-04 where the weight normalization of Vd and Cl also demonstrated that gender effect was not significant ($p > 0.43$).

Race: For both studies, the number of subjects in each racial group was insufficient to conduct any meaningful analysis. In study AB-00-04, the demographic number of Caucasian, Black, Asian, Hispanic was 17:8:1:2 and for study AB-00-05 it was 19:2:0:7.

4.4 Extrinsic Factors

Is there any systemic interaction between ibuprofen and pseudoephedrine when both drugs are administered in combination as a Liquigel?

Yes there was an interaction observed between ibuprofen and pseudoephedrine when both drugs were administered to healthy adults in combination as a liquigel compared to single ingredient drug products. Reproduced in the tables below is a summary of the pharmacokinetic parameters and 90% confidence intervals for ibuprofen and pseudoephedrine from the combination products and single ingredient products:

Table 5. Ibuprofen Pharmacokinetic Parameters and 90% Confidence Intervals

Parameter	Mean (CV%) (N = 27)				
	Advil Cold and Sinus Liquigel (Treatment A)	Advil Liquigels (Treatment B)	Advil Cold and Sinus Tablets (Treatment D)	Ratio of A/B*(%) and [90% CI]	Ratio of A/D*(%) and [90% CI]
AUCL (mcg.h/mL)	106.47 (25.42)	103.82 (22.39)	107.94 (23.93)	104.66	98.09
AUCinf (mcg.h/mL)	108.42 (24.83)	106.15 (22.60)	110.69 (23.99)	103.42	97.86
Cmax (mcg/mL)	35.28 (38.71)	38.83 (23.91)	29.11 (29.69)	90.68	124.93
Tmax (h)	1.10 (82.37)	0.80 (40.88)	2.20 (64.25)		

*Ratio of least squares means of log transformed values of Treatment A and B or A and D

Table 6. Pseudoephedrine Pharmacokinetic Parameters and 90% Confidence Intervals

Parameter	Mean (CV%) (N = 27)				
	Advil Cold and Sinus Liquigel (Treatment A)	Sudafed Liquid Medication (Treatment C)	[2]Advil Cold and Sinus Tablets (Treatment D)	Ratio of A/C*(%) and [90% CI]	Ratio of A/D*(%) and [90% CI]
AUCL (ng.h/mL)	2023.49 (32.03)	1875.22 (29.10)	2048.47 (30.18)	111.47	93.59
AUCinf (ng.h/mL)	2134.90 (35.09)	1952.11 (30.68)	2156.99 (33.03)	108.13	94.42
Cmax (ng/mL)	219.04 (36.11)	188.59 (24.55)	228.60 (29.62)	116.73	93.90
Tmax (h)	2.40 (50.43)	2.15 (46.58)	1.86 (60.33)		

*Ratio of least squares means of log transformed values of Treatment A and C or A and D; [2]n=25

The results as shown in the table above indicate that for AUC the 90% CI for ibuprofen and pseudoephedrine were within the acceptable limits for bioequivalence (i.e. 80-125%) demonstrating similar extent of absorption. The rate of absorption (Cmax) of pseudoephedrine was also similar to that of Advil Cold and Sinus tablet. However the rate of absorption (mean Cmax) of ibuprofen from the combination liquigel is slightly lower (~ 9%) than that of Advil liquigels and, higher (~21.2%) than that for Advil Cold and Sinus tablet. Also the rate of absorption (mean Cmax) of pseudoephedrine from the combination liquigel is higher (~16.2%) than that of Sudafed.

The mean Tmax for ibuprofen from the combination liquigel was similar to that of the individual component product, but faster than that of the combination tablet. However, the mean Tmax for pseudoephedrine from the combination tablet was similar to that of the individual component but slower than that of the combination tablet. Therefore these results suggest that the rate of absorption of either component was affected by the presence of the other. The clinical significance of this finding for ibuprofen would be related to efficacy and for pseudoephedrine it would be related to safety.

The applicant referenced the following approved NDA's for support of the safety and efficacy of ibuprofen and ibuprofen/pseudoephedrine combination: NDA 18-989 (Advil® tablets/caplets), NDA 19-771 (Advil ® Cold and Sinus tablets/caplets), and NDA 20-402 (Advil Liquigels®). Since the Cmax for ibuprofen obtained with the combination liquigel was between that of two already approved products (single ingredient liquigel and combination tablet). The difference in the rate of absorption for ibuprofen is unlikely to be clinically significant in terms of efficacy.

For Pseudoephedrine although the Cmax reported for the Advil Cold and Sinus combination product was higher than that of Sudafed it was similar to that of Advil Cold and Sinus tablet. During discussions with the medical reviewer (Dr. A. Segal) I was informed that the global safety data for the Advil Cold and Sinus tablet was not different from that of Sudafed. Since the Cmax for pseudoephedrine in the present study for the combination liquigel was bioequivalent to that of the combination tablet, it is unlikely that the incidence rates for adverse experiences would be higher for the liquigel.

Therefore the higher pseudoephedrine Cmax obtained with the combination product does not appear to have a clinical significance in terms of safety.

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?

The presence of food resulted in a decrease in the rate of absorption of ibuprofen from Advil Cold and Sinus liquigel. However there was no effect on the extent of absorption for ibuprofen or the bioavailability of pseudoephedrine HCl. Reproduced in the tables below is a summary of ibuprofen pharmacokinetic parameters and the 90%CI following the fed and fasted treatments.

Table 7. Ibuprofen Pharmacokinetic Parameters and 90% Confidence Intervals in the Fed and Fasted State

Parameter	Mean (CV%) (N = 27)		
	Fasted (Treatment A)	**Fed (Treatment B)**	**Ratio of B/A*(%) and [90% CI]**
AUCL (mcg.h/mL)	123.62 (20.61)	103.95 (20.69)	84.01
AUCinf (mcg.h/mL)	125.98 (21.22)	106.84 (20.54)	84.81
Cmax (mcg/mL)	41.21 (25.40)	28.64 (28.50)	69.76
Tmax (h)	0.89 (76.42)	1.69 (50.58)	

* Ratio of least squares means of log transformed values of Treatment A and B

The data in the table above shows that under fed conditions the mean Cmax of ibuprofen was decreased by ~ 30.5 % as compared to fasting conditions. Therefore this implies that in the presence of food there is the possibility of a delay in the onset of pain relief. Also since peak plasma levels are correlated with the degree of analgesia this reduction in plasma levels may be significant. Since the Cmax value obtained for the fed state with the liquigel (28.64±28.5 mcg/mL) is similar in value to that obtained with the approved combination tablet (29.11± 29.69 mcg/mL) in the fasted state in the other study in this application (study # AB-00-04), it is unlikely to be clinically relevant.

An evaluation of the individual plasma-concentration time profiles indicates a 15-30 minute delay in the onset of pain relief due to the presence of food. Also, the data indicated a delay of about 50 minutes in the mean Tmax (or possibly time of peak analgesic effect) of ibuprofen in the presence of food. However, this is only suggestive when one considers the high variability associated with the values. Also, an evaluation of the individual data further supports this as shown in the histogram below:

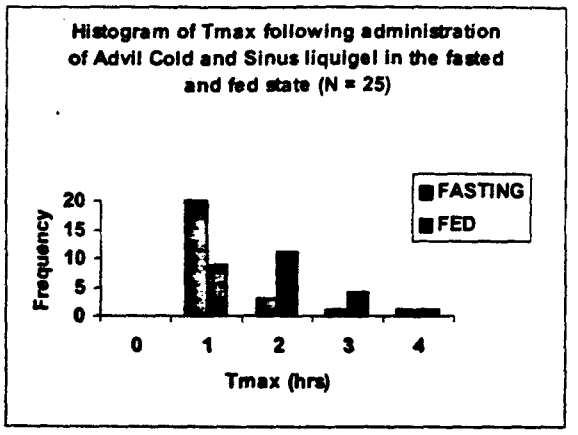


Table 8. Pseudoephedrine Pharmacokinetic Parameters and 90% Confidence Intervals in the Fed and Fasted State

Parameter	Mean (CV%) (N = 25)		
	Fasted (Treatment A)	Fed (Treatment B)	Ratio of A/C*(%) and [90% CI]
AUCL (ng.h/mL)	2289.38 (22.76)	2357.93 (21.04)	103.40
AUCinf (ng.h/mL)	2424.16 (25.87)	2486.30 (23.69)	103.09
Cmax (ng/mL)	254.40 (21.26)	265.60 (25.05)	103.45
Tmax (h)	2.06 (38.23)	3.04 (42.76)	

*Ratio of least squares means of log transformed values of Treatment A and B or A and D; [2]n=25

The data in the table above shows that there was no observed food effect on the rate and extent of absorption of pseudoephedrine HCl from Advil Cold and Sinus liquigel because the 90% CI for AUC and Cmax were within the acceptable limits (80-125%).

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 Cold and Sinus Liquid Suspension is reproduced in the Table below:

Table 9: Dissolution Method and Specifications

Apparatus	USP Apparatus I Type- Baskets
Speed	150 RPM
Media	900 mL 50mM phosphate buffer, pH 7.2
Temperature	37.0°C ± 0.5°C
Sampling Time Points	10, 20 and 30 minutes
Number of Units	12
Method of Analysis	
Specification	Q =

The applicant has proposed a dissolution speed of [redacted] however they have not provided any justification for the choice of this [redacted] speed. In general mild agitation conditions (usually 50-100 rpm) for the basket method, is recommended during dissolution testing to allow for maximum discriminating power and to detect products with poor in vivo performance. Following discussions with the chemistry reviewer (Dr. R. Puttagunta) it was decided that the sponsor should provide a scientific rationale and adequate data to support their proposed [redacted]

Table 10: Dissolution Results

	Mean Percent Dissolved (SD) N = 12 (Time in Minutes)	
	Ibuprofen-Pseudoephedrine HCl Clinical Study Formulation (WH-0686-0008)	
Time (minutes)	Ibuprofen	Pseudoephedrine HCl
10	[redacted]	[redacted]
20	[redacted]	[redacted]
30	[redacted]	[redacted]

A preliminary review of the dissolution results using the proposed method as shown in the table above demonstrate that for the product formulation evaluated, [redacted] of ibuprofen and pseudoephedrine HCL were dissolved in 20 minutes. It is very odd that at 10 minutes [redacted] of the drug product had dissolved. Both formulations passed the applicant's dissolution specifications of [redacted] Provided there is adequate justification for the choice of [redacted], it appears that a [redacted] specification of [redacted] instead of [redacted] would be more appropriate for ensuring lot-to-lot uniformity of the drug product.

4.6 Analytical

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

[redacted]

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

[redacted]

Reproduced in the Table below are the analytical validation results for ibuprofen and pseudoephedrine:

Table 11: Analytical Validation Results

Compound		Ibuprofen	Pseudoephedrine
Accuracy	*Within-Day*		
	Between-Day		
Precision (CV%)	*Within-Day*		
	Between-Day		
Standard curve range			
Sensitivity (LOQ)			
Selectivity			
Stability			

The method validation results as shown in the Table above demonstrates that the analytical method used for quantitative measurement of ibuprofen and pseudoephedrine in human plasma are reliable and reproducible for the intended use. However, the applicant only provided a brief summary of the operational description of the analytical method. The applicant did not provide any information on the extraction processes and the identity of the internal standard used in the assay development or validation experiment. In the future this information should be included in the assay development report.

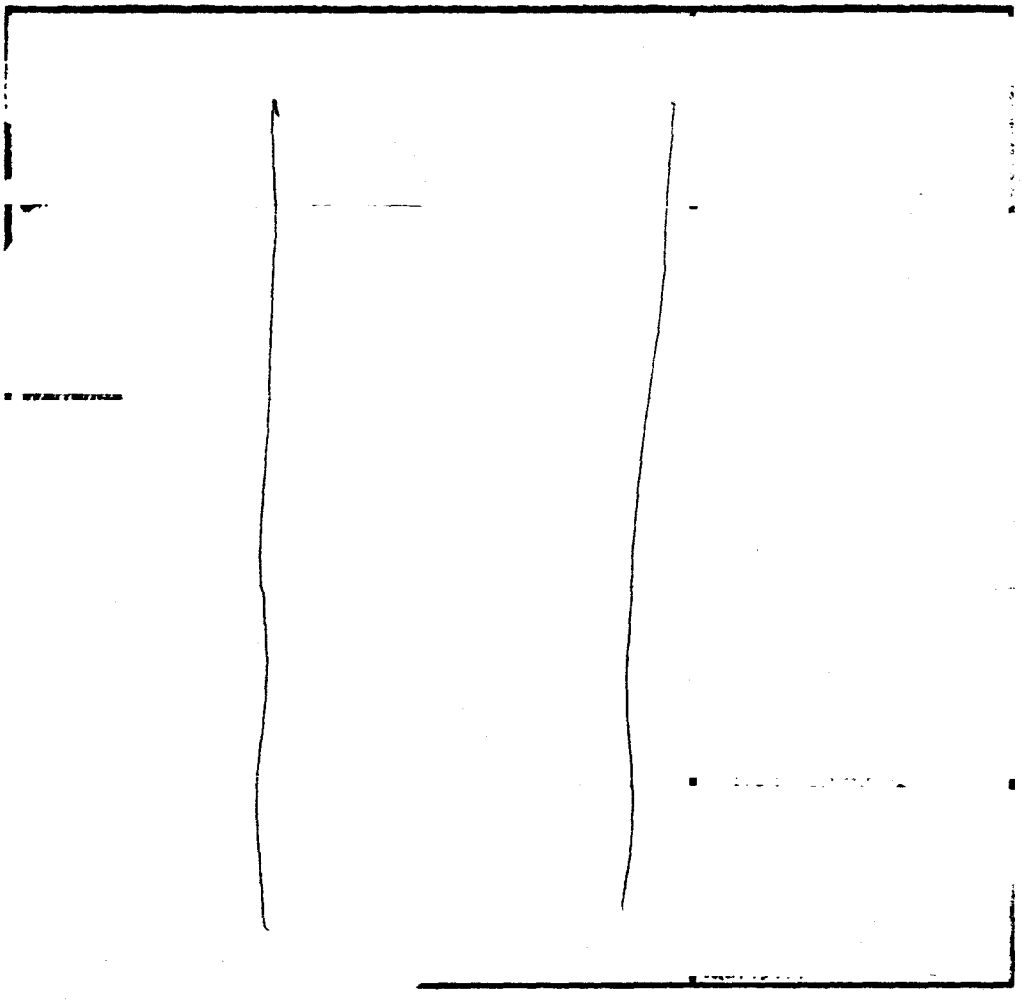
5 Detailed Labeling Recommendations

The applicant addressed the effect of food on Cmax observed with ibuprofen in Advil Cold and Sinus liquigels in their proposed labeling by including the following statement under the directions: **and, also "Take with food or milk if stomach upset occurs".** During discussions with the medical reviewer (Dr. A. Segal) it was concluded that although the food effect might result in a 15-30 minute delay in the onset of analgesia, this time-frame would not be considered to be a therapeutic disadvantage in this case since the patient would still get relief within an hour. The main concern here was safety with regards to administering NSAID's on an empty stomach due to the higher possibility of GI toxicity. Ideally one would then expect the patient to stop taking the medication if stomach upset occurs. Therefore, following an internal meeting in HFD-560 it was decided that it would be

better if the applicant modified their proposed labeling by simply stating —
— This instruction is consistent with that currently on NSAID containing OTC products in the marketplace.

6 Appendix

6.1 Proposed Annotated labeling



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Draft Labeling
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6.2 Individual Study Reviews

NDA 21-374: Study No. AB-00-04 Synopsis

Title of Study: Advil Cold & Sinus Liquigel Relative Bioavailability Study

Investigator: [redacted]

Study Centers: [redacted]

Study Period: November 14, 2000 — December 17, 2000

Phase of Development: Phase II

Objectives: To compare the rate and extent of absorption of ibuprofen and pseudoephedrine hydrochloride from an Advil Cold & Sinus Liquigel formulation (ibuprofen 200 mg/ pseudoephedrine hydrochloride 30 mg/liquigel) to Advil Liqui-gel ® (ibuprofen 200 mg/liquigel), Children's Sudafed ® Nasal Decongestant Liquid Medication (pseudoephedrine hydrochloride 15 mg/5 mL), and Advil Cold & Sinus tablets (ibuprofen 200 mg/pseudoephedrine hydrochloride 30 mg/tablet).

Number of Subjects (planned/analyzed):

Twenty-eight healthy, non-smoking volunteer subjects (20 males (71.4%) and 8 females (26.8%)) were enrolled; 27 subjects completed all four treatment periods. The average age, weight, and height of the population were 32.8 years (range: 20 to 44 years), 163.4 pounds (range: 108 to 225 pounds), and 68.7 inches (range: 62 to 76 inches), respectively. The majority of the subjects were Caucasian (17 = 61%), followed by Black (8 = 29%), Hispanic (2 =7%), and Asian (1 =4%). One subject (111) dropped out after period 1 and was excluded from all primary pharmacokinetic analysis. In addition, some data from four subjects were excluded from the secondary pharmacokinetic analyses for ibuprofen (Subject # 107,119, 202, 204) and pseudoephedrine (Subject # 112, 202, 203, 205) due to pre-dosing ibuprofen levels above 0.200 mcg/mL and pseudoephedrine above 2.50 ng/mL *(i.e.,* above the minimum level of quantification).

Table 1: Subjects with pre-dose concentrations of ibuprofen:

Subject No.	Period	Treatment	Cmax (mcg/mL)	Pre-dose ibuprofen concentration (mcg/mL)	% of Cmax Value
107	III	A	49.5	0.558	1.13
119	IV	B	35.30	0.629	1.78
202	I, II, IV	B, D, A	49.0, 29.50, 48.10	0.283, 0.242, 0.215	0.58, 0.82, 0.45
204	III	A	55.80	0.235	0.42

Table 2: Subjects with pre-dose concentrations of pseudoephedrine

Subject No.	Period	Treatment	Cmax (mcg/mL)	Pre-dose ibuprofen concentration (mcg/mL)	% of Cmax Value
112	I, II, III	A, C, D	168, 163, 228	6.65, 8.08, 16.90	3.96, 4.96, 7.14
202	IV	A	412	16.50	4.00
203	II, III	C, D	223, 427	7.12, 5.58	3.19, 1.31
205	IV	A	193	3.75	1.94

The pre-dose concentrations of ibuprofen were less than 5% of the Cmax values in the corresponding subject, therefore, the data of the subjects could all be included in the PK calculations. The pre-dose concentrations of pseudoephedrine were less than 5% of the Cmax

values except for Subject 112, treatment D, therefore this subject should be excluded from the pharmacokinetic evaluations for this treatment.

Treatments: Once eligibility was determined, subjects received one of the four treatments following an overnight fast of 10 hours (10 PM to 8 AM): *Treatment A:* Two Advil Cold & Sinus Liquigel (ibuprofen 200 mg/pseudoephedrine hydrochloride 30 mg/liquigel) (Whitehall-Robins Healthcare Batch No. — WH-0686-0008-002, [redacted] *Treatment B:* Two Advil Liqui-gel (ibuprofen 200 mg/liquigel) (Whitehall-Robins Healthcare Lot No. 3001515;); *Treatment C:* 20 mL Children's Sudafed Nasal Decongestant Liquid Medication (pseudoephedrine hydrochloride 15 mg/5 mL) (Warner-Lambert Consumer Healthcare Lot No. 47210L); *Treatment D:* Two Advil Cold & Sinus Tablets (ibuprofen 200 mg/pseudoephedrine hydrochloride 30 mg/tablet) (Whitehall-Robins Healthcare Lot No. 3001335). Treatment was administered on four separate occasions separated by 7 days, the order of which was randomly chosen.

Pharmacokinetic Blood Sampling: During all treatment periods, blood (12 mL for TX A & D and, 7 mL for TX B & C) was drawn before dosing and at specified intervals up to 24 hours following dosing: 15, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose. Each blood sample was [redacted] The plasma was stored at -20°C until shipped to [redacted] for the assay of ibuprofen and pseudoephedrine HCl.

Analytical Methodology: Pseudoephedrine hydrochloride plasma levels were determined using [redacted] Ibuprofen plasma levels were determined using [redacted]

Pharmacokinetic Parameters and Statistical Methods: AUCL, AUCI, and Cmax (both log transformed and untransformed) were analyzed for differences among treatments using analysis of variance (ANOVA) with effects for gender, subject (gender), period, treatment, and treatment-by- gender interaction. The gender effect was tested using subject (gender) as the error term, and using sequential (type I) sums of squares. If the gender effect or the treatment-by-gender interaction was, in general, significant ($p < 0.10$), additional analyses for Vd and Cl adjusting for weight were performed. If the gender effect or the interaction was still present, AUCL, AUCI, and Cmax, both log transformed and untransformed, would also be analyzed by the gender subgroups. A 90% two-sided confidence interval for the relative bioavailability relative to the reference, was calculated for the following pairs of treatments: Advil Cold & Sinus Liquid-Gel (Treatment A) vs. Advil Liquid-Gel (Treatment B, reference); Advil Cold & Sinus Liquid-Gel (Treatment A) vs. Children's Sudafed Nasal Decongestant Liquid (Treatment C, reference); and Advil Cold & Sinus Liquid-Gel (Treatment A) vs. Advil Cold & Sinus Tablet (Treatment D, reference). For each of the above comparisons, bioequivalence was declared if the 90% two-sided confidence interval for the ratio was between 80% and 125% for log transformed AUCL and Cmax data. The applicant also carried out a secondary analysis excluding the data from subjects with pre-dose plasma concentrations.

Results:

Figure 1. AB-00-04 Mean Ibuprofen (mcg/mL) Plasma Concentration Over Time (n=27)

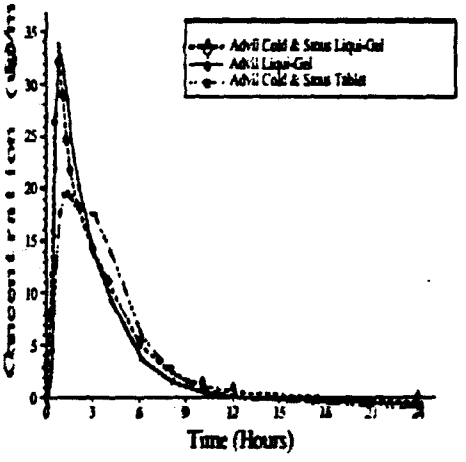
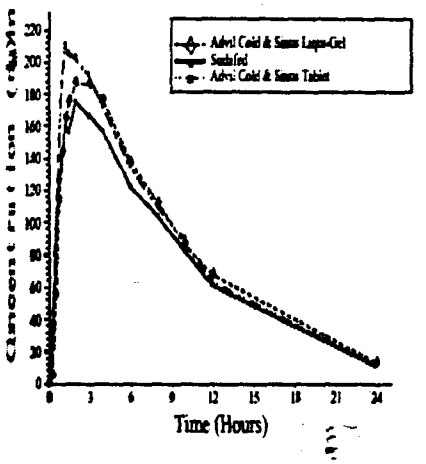


Figure 2. AB-00-04 Mean Pseudoephedrine Hydrochloride (ng/mL) Plasma Concentration Over Time (n=27)



Pharmacokinetic Parameters

Ibuprofen

Summary of Mean Pharmacokinetic Parameters for Ibuprofen (n=27)

[1]Parameters	[2]Formulation (Arithmetic Mean ±CV%)		
	A	B	D
C_{max} (mcg/mL)	35.28 (38.71)	38.83 (23.91)	29.11 (29.96)
$AUC_{(0-\infty)}$ mcg*hr/mL)	108.42 (24.83)	106.15 (22.60)	110.69 (23.99)
$AUC_{(0-24)}$ mcg*hr/mL)	106.47 (25.42)	103.82 (22.39)	107.94 (23.93)
T_{max} (hr)	1.10 (82.37)	0.80 (40.88)	2.20 (64.25)
Cl (L\ hr)	3.90 (23.52)	3.95 (22.34)	3.82 (23.96)
Vd (L)	18.44 (92.11)	12.55 (25.67)	13.13 (42.92)
$T_{1/2}$ (hr)	3.27 (76.82)	2.25 (26.36)	2.44 (45.20)
Kel (1/h)	0.28 (37.53)	0.33 (21.46)	0.32 (26.24)

[1] For AUC inf, Cl, Vd, T1/2 and Kel, N = 26 for formulations A and B. [2]: Formulation A= Advil Cold and Sinus Liqui-gel; B=Advil Liqui-gel and D= Advil Cold and Sinus tablet

Parameter	N	Ratio of Least Squares Means (%)	Study Power	90% CI Specification 80-125% Lower	Upper
A versus B					
ln $AUC_{(0-24)}$	27	104.66	>99.9%		
ln $AUC_{(0-\infty)}$	26	103.42	>99.9%		
ln C_{max}	27	90.68	>82.36%		
A versus D					
ln $AUC_{(0-24)}$	27	98.09	>99.9%		
ln $AUC_{(0-\infty)}$	26	97.86	>99.9%		
ln C_{max}	26	124.93	>82.36%		

Ibuprofen Primary Analysis Results

The 90% confidence intervals for LnAUCL and LnAUCI were within the accepted limits for bioequivalence (80-125%) when comparing Advil Cold and Sinus Liquigel to both references demonstrating similar extent of absorption. However, Cmax for Advil Cold & Sinus Liquigel was lower (~0.16% outside the accepted limits) than that for the Advil Liquigel, but higher (~13.5% outside the accepted limits) than that for Advil Cold & Sinus Tablet. Since the mean Cmax of Advil Cold and Sinus Liquigel is higher (~ 18%) than that of the tablets (an already approved product), this difference (i.e.~ 13.5%) might not have much relevance clinically.

Pseudoephedrine

Summary of Mean Pharmacokinetic Parameters for Pseudoephedrine (n=27)

[1]Parameters	[2]Formulation (Arithmetic Mean ±CV%) A	C	D
C_{max} (ng/mL)	219.04 (36.11)	188.59 (24.55)	235.93 (31.97)
$AUC_{(0-\infty)}$ ng*hr/mL)	2134.90 (35.09)	1952.11 (30.68)	2195.36 (33.87)
$AUC_{(0-24)}$ ng*hr/mL)	2023.49 (32.03)	1875.22 (29.10)	2083.10 (30.97)
T_{max} (hr)	2.40 (50.43)	2.15 (46.58)	1.81 (60.72)
Cl (L\ hr)	30.67 (26.40)	33.30 (27.00)	30.20 (31.38)
Vd (L)	217.10 (26.07)	237.58 (25.54)	209.75 (24.94)
$T_{1/2}$ (hr)	5.03 (20.04)	5.02 (14.14)	4.99 (19.31)
Kel (1/h)	0.14 (18.71)	0.14 (13.76)	0.14 (17.13)

[1] For AUC inf, Cl, Vd, T1/2 and Kel, N = 26 for formulations A and B. [2]: Formulation A= Advil Cold and Sinus Liqui-gel; C=Sudafed and D= Advil Cold and Sinus tablet

Parameter	N	Ratio of Least Squares Means (%)	Study Power	90% CI Specification 80-125% Lower	Upper
A versus C					
ln $AUC_{(0-24)}$	27	108.13	>99.9%		
ln $AUC_{(0-\infty)}$	26	111.47	>99.9%		
ln C_{max}	27	116.73	>99.56%		
A versus D					
ln $AUC_{(0-24)}$	27	97.13	>99.9%		
ln $AUC_{(0-\infty)}$	26	98.02	>99.9%		
ln C_{max}	26	92.23	>99.56%		

Pseudoephedrine Primary Analysis Results

The 90% confidence intervals for AUCL and AUCI were within the accepted limits for bioequivalence (80-125%) when comparing Advil Cold and Sinus Liquigel to both references

demonstrating similar extent of absorption. The 90% interval for Cmax was also within the limits comparing to Advil Cold & Sinus Tablet demonstrating BE. However, the upper bound of the interval was outside (~1.2%) the accepted limit for comparison with Children's Sudafed Nasal Decongestant Liquid Medication. Since the mean Cmax of Advil Cold and Sinus Liqui-gel is lower (~8%) than that of the tablets (an already approved product), this difference (1.2%) might not have much relevance clinically.

Gender Effects:

For ibuprofen and pseudoephedrine hydrochloride a gender effect ($p<0.10$) was found for AUCL, AUCI, and Cmax (both untransformed and log transformed), CL and Vd (pseudoephedrine only). For pseudoephedrine hydrochloride, the gender differences in the pharmacokinetic parameters could be adjusted by weight normalization. However, for Ibuprofen, the gender effect was still significant for ibuprofen adjusted CL, although adjusted Vd was not, so the applicant did an additional analysis by gender subgroups and the results are presented below:

Ibuprofen

Table: Summary of Mean (CV%) Pharmacokinetic Parameters for Ibuprofen from Advil Cold and Sinus Liquigels in Gender Subgroups

Parameters	Males (N=19)	*Females (N = 7)
C_{max} (mcg/mL)	29.57 (36.54)	48.83 (19.87)
$AUC_{(0-\infty)}$ mcg*hr/mL)	102.81 (25.75)	123.67 (18.92)
$AUC_{(0-24)}$ mcg*hr/mL)	99.25 (26.44)	123.62 (17.57)
T_{max} (hr)	1.24 (84.82)	0.76 (14.86)
Cl (L\ hr)	4.11 (22.58)	3.34 (19.25)
Vd (L)	19.54 (99.04)	15.46 (51.91)
$T_{1/2}$ (hr)	3.26 (84.15)	3.30 (58.53)
Kel (1/h)	0.28 (36.72)	0.26 (42.52)

* N = 8 for AUC 0-24, Cmax and Tmax

The data in the table above indicates that the females have a higher Cmax and AUC and, a somewhat lower CL than the males.

Parameter	Males (N = 19) Ratio of Least Squares Means (%)	Study Power	90% CI Specification 80-125% Lower	Upper
A versus B				
ln $AUC_{(0-24)}$	97.98	>99.9%		
ln $AUC_{(0-\infty)}$	99.46	>99.9%		
ln C_{max}	79.07	>71.32%		
A versus D				
ln $AUC_{(0-24)}$	98.21	>99.9%		
ln $AUC_{(0-\infty)}$	99.10	>99.9%		
ln C_{max}	103.39	>71.32%		

Parameter	Females			90% CI Specification 80-125%	
	N	Ratio of Least Squares Means (%)	Study Power	Lower	Upper
A versus B					
ln $AUC_{(0-24)}$	8	111.78	>98.57%		
ln $AUC_{(0-\infty)}$	7	107.48	>98.73%		
ln C_{max}	8	104.38	>53.73%		
A versus D					
ln $AUC_{(0-24)}$	8	97.91	>98.57%		
ln $AUC_{(0-\infty)}$	7	97.06	>99.21%		
ln C_{max}	8	150.60	>53.73%		

For the males the data demonstrated BE between Advil Cold and Sinus Liqui-gel and Advil Cold and Sinus tablets. However, the data only demonstrated similarity between Advil Cold and Sinus Liquigel and Advil Liqui-gel for the extent of absorption but not the rate. The 90% CI for lower bound of the interval for Cmax was outside (~11.62%) the accepted limits.

For the females the data demonstrated BE between Advil Cold and Sinus Liqui-gel and Advil Liquigel. However, the data only demonstrated similarity between Advil Cold and Sinus Liqui-gel and Advil Cold and Sinus Tablets for the extent but not the rate. The 90% CI for the lower bound of the interval for Cmax was outside (~46-58%) the accepted limits. The data within each gender were, in general, consistent with each other in that gender differences were only observed with the rate of absorption and not the extent. The gender differences appeared to be more pronounced in the females than the males, probably due to the smaller sample size and thus a lower power. The applicant stated that the gender effect of ibuprofen has not been noted in the literature, therefore given its long use, this difference may be an artifact of the design of the study and, therefore unlikely to be clinically significant.

Secondary Pharmacokinetic Analysis

Secondary pharmacokinetic analyses were carried out excluding some data from subjects with pre-dosing plasma concentrations of ibuprofen and pseudoephedrine. The results of the secondary analysis were consistent with that of the primary analysis and the conclusions remained unchanged.

Conclusions: For ibuprofen Advil Cold & Sinus Liquigel are similar to the reference standards in terms of extent of absorption of ibuprofen but not the rate. For pseudoephedrine Advil Cold & Sinus Liqui-gel are bioequivalent to Advil Cold and Sinus tablet. Advil Cold and Sinus liquigel is similar to Sudafed liquid suspension for the extent but not the rate (it exceeds the suspension) of absorption of extent of absorption of ibuprofen.

NDA 21-374: Study No. AB-00-05 Synopsis

Title of Study: Advil ® Cold & Sinus Liquigel ® Food Effects Bioavailability Study

Investigator: ———

Study Centers:

78704-7016. Analytical Site: ———

Study Period: November 10, 2000 — November 19, 2000

Phase of Development: Phase II

Objectives: To compare the rate and extent of absorption of ibuprofen and pseudoephedrine hydrochloride from an Advil Cold & Sinus Liquigel formulation (ibuprofen 200 mg/pseudoephedrine hydrochloride 30 mg) under fed and fasted conditions.

Study Design: Single-center, randomized, open-label, single-dose, and 2-way crossover study

Treatments: Prior to the start of the study, there was a complete review of all inclusion/exclusion criteria to determine eligibility for enrollment. Once eligibility was determined, subjects received one of the two treatments: *Treatment A:* Two Advil Cold & Sinus Liquigels - fasted (ibuprofen 200 mg/ pseudoephedrine hydrochloride 30 mg/liquigel) (Whitehall-Robins Healthcare lot No.WH-0686-0008-002); *Treatment B:* Two Advil Cold & Sinus Liquigels – fed (ibuprofen 200 mg/ pseudoephedrine hydrochloride 30 mg/liquigel) (Whitehall-Robins Healthcare lot No.WH-0686-0008-002). Each treatment was separated by no less than five days and no more than seven days and the sequence of treatments was randomized.

Number of Subjects (planned/analyzed):

Twenty-eight healthy volunteer subjects (14 males (50.0%) and 14 females (50.0%)) were enrolled; 25 subjects completed both treatment periods. The average age, weight, and height of the population were 24.86 years (range: 18 to 44 years), 151.89 pounds (range: 110 to 192 pounds), and 68.61 inches (range: 62 to 75 inches), respectively. The majority of the subjects were Caucasian (19 = 67.86 %), followed by Hispanic (7 =25 %) and Black (2 = 7.14%).

Three subjects (312, 404, and 408) were excluded from the primary pharmacokinetic analyses. One subject (404) was randomized to be fed in Period I and then fasted in Period II but did not return for Period II. The other two subjects had protocol violations. Subject 312 did not consume the standardized breakfast within the allotted time. Per protocol, subjects were required to consume the standardized breakfast approximately 20 minutes prior to dosing. For this subject, the time between consuming breakfast and dosing was 30 minutes. Subject 408 had Period II pre-dosing concentrations for ibuprofen and pseudoephedrine hydrochloride that were above acceptable levels (0.246 mcg/mL and 54.100 ng/mL respectively). For subject 312, ingestion of the meal 30 minutes before dosing is probably acceptable according to the Draft guidance for Food –Effect Bioavailability and Fed Bioequivalence Studies. For subject 408, the pre-dose concentration of 0.246 mcg/mL for ibuprofen is < 5% of the Cmax, therefore this is acceptable. However, the pre-dose concentration of 54.10 for pseudoephedrine is 13.7% of Cmax, since this is > 5% it is unacceptable. The applicant however performed a secondary pharmacokinetic analysis including subjects 312 and 408. Based on the aforementioned only the secondary analysis data for ibuprofen is acceptable.

Pharmacokinetic Blood Sampling: Blood (12 mL) samples were taken by venipuncture or by venous catheter, into ——— A) at: pre-dose, and 15, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose. Approximately 360 mL of blood was drawn during the two treatment periods excluding the blood sample required for the pre-study clinical laboratory evaluations. Each blood sample was

The plasma samples were stored at -20 °C or lower until shipped to ——— and assayed for racemic ibuprofen or pseudoephedrine hydrochloride.

Analytical Methodology: Pseudoephedrine hydrochloride plasma levels were determined using

Pharmacokinetic Parameters and Statistical Methods: AUCL, AUCI, and Cmax (both log transformed and untransformed) were analyzed for differences among treatments using analysis of variance (ANOVA) with effects for gender, subject (gender), period, treatment, and treatment-by- gender interaction. The gender effect was tested using subject (gender) as the error term, and using sequential (type I) sums of squares. If the gender effect or the treatment-by-gender interaction was, in general, significant ($p < 0.10$), additional analyses for Vd and Cl adjusting for weight were performed. A 90% two-sided confidence interval for the relative bioavailability of test (fed) vs. the reference (fasted), was calculated. Bioequivalence was declared if the 90% two-sided confidence interval for the ratio was between 80% and 125% for log transformed AUCL and Cmax data.

Results: Plasma Concentration-Time profiles

Figure 1. AB-00-05 Mean Ibuprofen (mcg/mL) Plasma Concentration Over Time

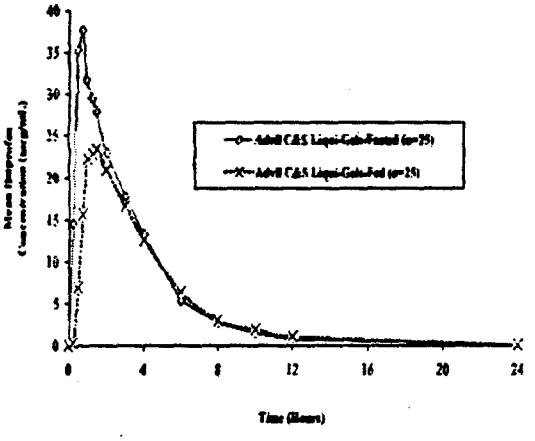
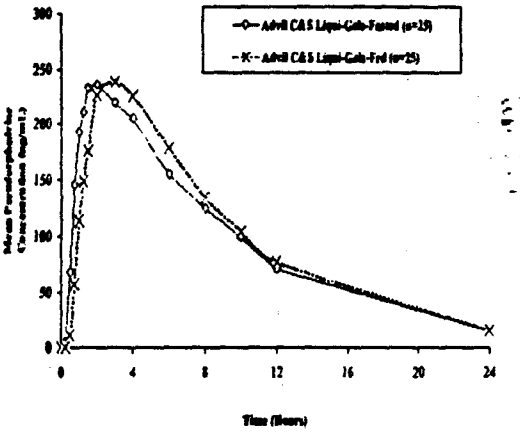


Figure 2. AB-00-05 Mean Pseudoephedrine Hydrochloride (ng/mL) Plasma Concentration Over Time



Pharmacokinetic Parameters

Ibuprofen

Summary of Mean Pharmacokinetic Parameters for Ibuprofen (N=25)

Pharmacokinetic Parameters	[1]Formulation (Arithmetic Mean (CV%))	
	A (Fasted)	**B (Fed)**
C_{max} (mcg/mL)	40.32 (25.36)	28.36 (29.45)
$AUC_{(0-\infty)}$ mcg*hr/mL)	125.75 (22.11)	105.42 (21.03)
$AUC_{(0-24)}$ mcg*hr/mL)	123.35 (21.48)	102.49 (21.14)
T_{max} (hr)	0.91 (77.31)	1.72 (51.01)
Cl (L\ hr)	3.36 (27.32)	3.98 (24.61)
Vd (L)	10.76 (29.37)	12.86 (26.14)
$T_{1/2}$ (hr)	2.31 (39.95)	2.29 (27.17)
Kel (1/h)	0.32 (21.59)	0.32 (22.54)

[1] Formulation A= Advil Cold and Sinus Liqui-gel (fasted); B=Advil Cold and Sinus Liqui-gel (fed).

Pharmacokinetic Parameter	(N = 25) Ratio of Least Squares Means (%)	Study Power	90% CI Specification (80-125%) Lower	Upper
A versus B				
ln $AUC_{(0-24)}$	83.10	>99.9%		
ln $AUC_{(0-\infty)}$	83.91	>99.9%		
ln C_{max}	70.64	>75.83%		

Ibuprofen Primary Analysis Results

The lower bound of the 90% confidence interval for LnAUCL, LnAUCI and LnCmax were outside the accepted limits for bioequivalence (80%) indicating that the rate and extent of ibuprofen absorption under fed conditions was less than under fasted conditions.

Pseudoephedrine

Summary of Mean Pharmacokinetic Parameters for Pseudoephedrine (N=25)

[1]Parameters	[1]Formulation (Arithmetic Mean (SD)) A	B
C_{max} (ng/mL)	254.40 (21.26)	265.60 (25.05)
$AUC_{(0-\infty)}$ ng*hr/mL)	2424.16 (25.87)	2486.30 (23.69)
$AUC_{(0-24)}$ ng*hr/mL)	2289.38 (22.76)	2357.93 (21.04)
T_{max} (hr)	2.06 (38.23)	3.04 (42.76)
Cl (L\ hr)	26.30 (24.26)	25.48 (23.64)
Vd (L)	187.86 (18.86)	173.45 (20.11)
$T_{1/2}$ (hr)	5.14 (24.27)	4.88 (25.37)
Kel (1/h)	0.14 (20.21)	0.15 (19.91)

[1] Formulation A= Advil Cold and Sinus Liqui-gel (fasted); B=Advil Cold and Sinus Liqui-gel (fed).

Pharmacokinetic Parameter	(N = 25) Ratio of Least Squares Means (%)	Study Power	90% CI Specification 80-125% Lower	Upper
A versus B				
ln $AUC_{(0-24)}$	103.40	>99.9%		
ln $AUC_{(0-\infty)}$	103.09	>99.9%		
ln C_{max}	103.45	>99.9%		

Pseudoephedrine Primary Analysis Results

The results showed that the 90% confidence intervals for both LnAUCL and LnCmax were within the accepted limits for bioequivalence indicating that the fasted and fed conditions were bioequivalent with respect to the rate and extent of pseudoephedrine hydrochloride absorption.

Gender Effects

For pseudoephedrine hydrochloride a statistically significant gender effect ($p<0.10$) was found for AUCL, and Cmax (both untransformed and log transformed), however this was adjusted by weight normalization suggesting that the gender differences seen with the AUCL and Cmax parameters are likely due to men generally weighing more than women.

Secondary Pharmacokinetic Analysis

Secondary pharmacokinetic analyses were carried out including data from 2 subjects with pre-dosing plasma concentrations of ibuprofen and pseudoephedrine HCl (subject # 408) and subject # 312 (who ate standardized breakfast within 30 minutes instead of 15-18 minutes as per protocol).

Ibuprofen

Summary of Mean Pharmacokinetic Parameters for Ibuprofen (N=27)

Pharmacokinetic Parameters	[1]Formulation (Arithmetic Mean (SD))	
	A	B
C_{max} (mcg/mL)	41.21 (25.40)	28.64 (28.50)
$AUC_{(0-\infty)}$ mcg*hr/mL)	125.98 (21.22)	106.84 (20.54)
$AUC_{(0-24)}$ mcg*hr/mL)	123.62 (20.61)	103.95 (20.69)
T_{max} (hr)	0.89 (76.42)	1.69 (50.58)
Cl (L\ hr)	3.34 (26.48)	3.93 (24.57)
Vd (L)	10.59 (29.30)	12.60 (26.67)
$T_{1/2}$ (hr)	2.28 (39.27)	2.27 (26.51)
Kel (1/h)	0.33 (21.10)	0.32 (21.62)

[1] Formulation A= Advil Cold and Sinus Liqui-gel (fasted); B=Advil Cold and Sinus Liqui-gel (fed).

Pharmacokinetic Parameter	(N = 27)		90% CI Specification 80-125%	
	Ratio of Least Squares Means (%)	Study Power	Lower	Upper
A versus B				
ln $AUC_{(0-24)}$	84.01	>99.9%		
ln $AUC_{(0-\infty)}$	84.81	>99.9%		
ln C_{max}	69.76	>80.09%		

The results showed that the 90% confidence interval for LnAUCL ( ) was within the accepted limits for bioequivalence when data from the additional two subjects are included. The results for LnCmax ( ) were however still outside the acceptable limits.

Pseudoephedrine

The results of the secondary analysis for pseudoephedrine HCL were consistent with that of the primary analysis.

Conclusions: The presence of food decreases the rate of absorption of ibuprofen from the ibuprofen/pseudoephedrine hydrochloride liquigel formulation. However, the presence of food had no effect on the rate and extent of absorption of pseudoephedrine hydrochloride from the ibuprofen/pseudoephedrine hydrochloride liquigel formulation.

Labeling Comments: The effect of food was addressed in the proposed labeling as follows:

Drug Facts

Directions

- adults and children 12 years of age and over:....
- —————

This labeling appears ambiguous and is under discussion with the clinical division.

6.2.4. Qualitative/Quantitative Composition Statement for the Study formulation of Advil Cold & Sinus Liqui-gel (WH-0686-0008-002)

Qualitative/Quantitative Composition Statement

Component	mg/liquigel	kg/batch
Gelatin Shell		
Gelatin, NF [illegible]		
Purified Water, USP [b]	low	
FD & C Red No. 40	?	
D & C Yellow No. 10	?	
	low	
	low	
	low	
	low	
Total Shell Weight (dried) [c]		
Fill Material		
Ibuprofen, USP	200	
Pseudoephedrine HCL USP	30.0	
Potassium Hydroxide, NF		
Polyethylene Glycol 600, NF (Low Aldehyde)		
Purified Water, USP		
	low	
Total Fill Weight (dried) [f]		
Total Liquigel Weight (dried)		

6.3 OCPB Filing/Review Form

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

General Information About the Submission

	Information		Information
NDA Number	21-374	Brand Name	Advil® Cold and Sinus Liquigels
OCPB Division (I, II, III)	III	Generic Name	Ibuprofen 200mg and Pseudoephedrine 30 mg
Medical Division	HFD-550	Drug Class	Analgesic/Antipyretic and Nasal decongestant
OCPB Reviewer	Abi Adebowale	Indication(s)	OTC use in temporarily relieving these symptoms of the common cold, sinusitis, or flu: headache, fever, nasal congestion, body aches and pains
OCPB Team Leader	Dennis Bashaw	Dosage Form	Liqui-Gels
IND Number	[redacted]	Dosing Regimen	1-2 capsules Q 4-6 hrs for adults and children ≥ 12 years old
Date of Submission	30th July 2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	1st April , 2002	Sponsor	Whitehall-Robins Healthcare
PDUFA Due Date	30th May, 2002	Priority Classification	3S
Division Due Date	30th April, 2002		

Clin. Pharm. and Biopharm. Information

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

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:	X	1A		
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		8		Gender Effect, Pk-PD Ibuprofen
Total Number of Studies	[redacted]	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?	**Not Yet**	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 clinically relevant?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale (08/08/01)**	
Secondary reviewer Signature and Date		

CC: NDA 21-373, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-550(B. Gould), HFD-880(D. Bashaw, J.Lazor, A. Selen), CDR

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

/s/

Abi Adebowale
4/10/02 10:19:51 AM
BIOPHARMACEUTICS

Dennis Bashaw
4/15/02 01:41:58 PM
BIOPHARMACEUTICS