

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-373

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number: 21-373 **Submission Date(s):** 06/18/01, 11/14/01, 02/08/02, 02/25/02

Brand Name: Children's Advil® Cold Suspension

Generic Name: Ibuprofen/Pseudoephedrine

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OCPB Division: DPEIII

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Sponsor: Wyeth Consumer Healthcare, Madison, NJ

Relevant IND(s): _____

Submission Type; Code: 3S

Formulation; Strength(s): Suspension, Ibuprofen (100 mg/5mL) and Pseudoephedrine HCl (15 mg/5 mL)

Indication: Analgesic/Antipyretic/Nasal Decongestant

1. Executive Summary

A combination tablet formulation of ibuprofen 200 mg and pseudoephedrine hydrochloride 30 mg is currently marketed over-the-counter (OTC) by the applicant for use in adults and children ≥ 12 years as Advil® Cold and Sinus tablets/caplet, (NDA 19-771 approved in 1989). In this application the applicant is seeking approval for a formulation suspension of the combination of ibuprofen 100 mg and pseudoephedrine 15 mg/5 mL (Children's Advil® Cold Suspension), targeted at the pediatric population aged 2-11 years old. The proposed indication is also similar to that of the approved combination tablet (i.e. for use in temporarily relieving symptoms associated with the cold, sinus, and flu). This NDA is supported by two pharmacokinetic studies (AQ-99-02 and AQ-00-04). Study AQ-99-02 characterized the rate and extent of absorption, distribution and elimination of ibuprofen and pseudoephedrine from the combination suspension in healthy children aged 6-11 years old. Study AQ-00-04 was conducted to obtain pharmacokinetic data on the combination suspension in children aged 2-5 years old with an acute upper respiratory tract infection.

1.1 Recommendation

Based on the data submitted in NDA 21-373, the applicant has met the requirements outlined in 21 CFR 320 and their application is acceptable from a clinical pharmacology and biopharmaceutics perspective.

The applicant adequately described the pharmacokinetics of the two active ingredients, ibuprofen and pseudoephedrine following single dose administration of the combination suspension to healthy children aged 6-11 years old and symptomatic children aged 2-5 years old. A cross comparison of the data obtained from the studies for the two different age groups demonstrated that the rate and extent of absorption of ibuprofen and pseudoephedrine HCl obtained with the combination suspension were similar across age groups. The data also suggested that the younger age group had a higher clearance (after weight normalization) for both pseudoephedrine and ibuprofen. This finding although suggestive, due to the imbalance in the data, is supportive of the proposed dosing

The systemic exposure data demonstrated that the rate and extent of absorption of ibuprofen and pseudoephedrine in the combination suspension product was similar to those obtained for the individual components when administered to children aged 6-11 years old. The pharmacokinetic study in symptomatic children aged 2-5 years old demonstrated that the rate and extent of absorption of pseudoephedrine from the combination suspension were similar to those of pseudoephedrine hydrochloride administered alone. Therefore the systemic exposure data from both age groups showed that the rate and extent of absorption of either ibuprofen or pseudoephedrine was not affected by the presence of the other when administered as a combination suspension in children aged 2-11 years old.

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**APPEARS THIS WAY
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3. Summary of CPB Findings

Introduction and Background: The two active moieties in Children's Advil® Cold Suspension, are ibuprofen and pseudoephedrine. Ibuprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) that 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 aged 2 to under 12 years of age. Currently, there is only one pediatric ibuprofen/pseudoephedrine suspension marketed OTC by McNeil Consumer Healthcare (approved August 1, 2000, NDA 21-128).

Clinical Pharmacology: This NDA is supported by two pharmacokinetic studies (AQ-99-02 and AQ-00-04). The applicant also provided supporting literature on the pharmacokinetics and bioavailability of ibuprofen and pseudoephedrine in children. Study AQ-99-02 characterized the rate and extent of absorption, distribution and elimination of ibuprofen and pseudoephedrine from the combination suspension in healthy children aged 6 -11 years. The treatments evaluated were

mg/5 mL), Children's Advil® Oral Suspension (Ibuprofen 100 mg/5 mL) and Children's Sudafed Nasal Decongestant Liquid Medication (pseudoephedrine HCl 15 mg/5 mL). The results of this study demonstrated that the rate and extent of absorption of ibuprofen and pseudoephedrine from the combination suspension were similar to those obtained for the individual components. Therefore the rate and extent of absorption of either component was not affected by the presence of the other when administered to children aged 6-11 years old.

Study AQ-00-04 was conducted to obtain pharmacokinetic data on the combination suspension in children aged 2-5 years old with an acute upper respiratory infection. The treatments evaluated were

and Children's Sudafed Nasal Decongestant Liquid Medication (pseudoephedrine HCl 15 mg/5 mL). The results demonstrated that the rate and

extent of absorption and, the clearance of pseudoephedrine obtained for the combination suspension was similar to those obtained for pseudoephedrine alone in symptomatic children aged 2-5 years. Specifically, the estimated mean values of the PK parameters from the combination suspension were within $\pm 30\%$ of the corresponding estimated mean for the reference suspension PK parameters (pre-specified criteria agreed upon with the FDA).

A cross comparison of the pharmacokinetic parameters (AUC, C_{max} and CL) from study AQ-99-02 in healthy children (6-11 years old) and study AQ-00-04 in symptomatic children (2-5 years old) was conducted. The results of this cross comparison demonstrated that the rate and extent of absorption of ibuprofen and pseudoephedrine were similar across age groups. The results also suggested that the younger age group had a higher clearance after weight normalization.

In the pharmacokinetic studies, analysis for ibuprofen was by high performance liquid chromatography with ultraviolet detection and LC/MS/MS using positive ion turbo ionspray with multiple reaction monitoring (MRM) detection for pseudoephedrine. Both methods were found to be reproducible and accurate and, therefore acceptable for the intended use.

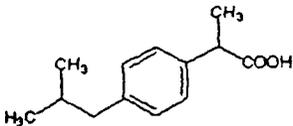
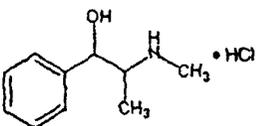
Biopharmaceutics: The clinical studies (AQ-99-02, AQ-99-03 and AQ-00-04) included in this submission utilized a combination formulation containing ibuprofen 110 mg / 5 ml and pseudoephedrine HCl 15 mg / 5 ml. In subsequent discussions between the Agency and the applicant it was agreed that the market formulation should contain 100 mg / 5 ml ibuprofen to be consistent with the currently marketed strengths, and that the data obtained with the 110 mg/15mg per 5 mL would be acceptable for extrapolating to the 100 mg/15 mg per 5 mL suspension. To support this the applicant submitted a secondary analysis of the pharmacokinetic data of ibuprofen normalized for the 100 mg/15mg per 5 mL dose, comparative dissolution data, and a comparative composition statement. The dissolution profiles of the two drug products for ibuprofen were similar (i.e. ~~_____~~). The dissolution results demonstrated that both formulations passed the applicant's dissolution specifications of NLT ~~_____~~. However, It appears that a tighter specification of ~~_____~~ minutes would be preferable for ensuring lot-to-lot quality of the drug product.

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?
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A. Highlights of the chemistry and physical-chemical properties of the drug substances in Children's Advil[®] Cold Suspension is 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. Ibuprofen is also 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 Children's Advil[®] Cold Suspension is a grape-flavored suspension that contains 100 mg ibuprofen and 15 mg pseudoephedrine HCl per 5 mL. Inserted below is the qualitative/quantitative composition statement for the suspension.

Ingredient	% W/V	Per 5 mL unit dose (mg)
Ibuprofen USP	2.00	100
Pseudoephedrine HCl USP	0.300	15.0
Xanthan Gum NF Pharm. Grade		
Microcrystalline Cellulose /		
Carboxymethylcellulose Sodium		
Polysorbate 80 NF		
Glycerin USP		
Sorbitol Solution		
Sucrose Beet NF		
Sodium Benzoate NF		
Disodium Edetate USP		
Citric Acid Hydrous USP		
Artificial Grape Flavor		
FD&C Red No. 40		
FD&C Blue No. 1		
Purified Water USP	Qs 100%	Qs 5 mL

What is the proposed dosage and route of administration?

The sponsor has proposed the following oral dose and dosing schedule to be repeated every 6 hours if needed, but not more than 4 times a day:

Weight (lb.)	Age (yr.)	Dose (tsp.)
under 24	under 2 yr.	ask a doctor
24-47	2 –5 yr.	1tsp
48 –95	6 –11 yr.	2 tsp.

The proposed dosing corresponds to the effective dose range of ibuprofen of 5-10 mg/kg of body weight with the older children receiving doses at the lower dose range and the younger children at the higher dose range.

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

A. Proposed mechanism of drug action(s):

Ibuprofen is an oral, 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 an orally administered 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.

B. Therapeutic Indications:

The proposed indications for Children's Advil® Cold Suspension are for the temporary relief of symptoms associated with the common cold, flu, or sinus, including nasal and sinus congestion, stuffy nose, headache, sore throat, minor aches and pains and, fever.

What efficacy and safety information contributed to the assessment of clinical pharmacology and biopharmaceutics study data?

The results of the safety study #AQ-99-03 and food effect data in NDA 19-771 were also used to assess the clinical pharmacology and biopharmaceutics data of this NDA.

In this NDA the applicant included the report of an actual use safety study (AQ-99-03) which was an open-label, multiple-dose, single treatment, two-center study of Children's Advil Cold Suspension in children with symptoms of an acute upper respiratory tract infection 2 to <12 years of age. The objective of this study was to characterize the adverse event profile of Children's Advil Cold Suspension in the target population. The applicant then referred to the clinical studies in approved NDA's (No. 18-989, 19-771, 20-589, 20-267, 20-812, and 20-944), sponsored by Whitehall Robins Healthcare for support of the safety and efficacy of ibuprofen and the combination of ibuprofen/pseudoephedrine hydrochloride.

4.2 General Clinical Pharmacology

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

Yes, the active moieties, ibuprofen and pseudoephedrine were appropriately identified and measured (refer to the Analytical Section in 4.6).

What are the pharmacokinetic parameters of ibuprofen and pseudoephedrine in Children's Advil® Cold Suspension and, how do these parameters in healthy children compare to those in pediatric patients?

Reproduced in Tables 1 and 2 below are the pharmacokinetic parameters of Ibuprofen and pseudoephedrine in healthy children aged 6 to < 12 years old (Study # AQ-00-02) and symptomatic children aged 2 to < 6 years old (Study # AQ-00-04).

Table 1. Comparison of the PK parameters [Mean (CV%)] of Ibuprofen from Children's Advil Cold® Suspension in healthy children and symptomatic children

Study #.	AQ-00-02 (Healthy Subjects)	AQ-00-04 (Symptomatic Children)
N	28	7
Age Range (years)	6-11	2-5
Study design	Crossover	Parallel
Single Dose (mg)	220	110
AUC _{inf} (µg.h/ml)	98.63 (25.16)	69.44 (17.83)
AUC ₀₋₁₂ (µg.h/ml)	97.69 (25.15)	68.40 (18.10)
*AUC ₀₋₉ (µg.h/ml)	96.02 (24.40)	72.70 (22.48)
CL/F (L/h)	2.36 (23.60)	1.63 (17.15)
CL/F (L/h*lb.)	0.03 (18.99)	0.04 (29.89)
T _{1/2} (h)	1.60 (13.59)	1.57 (17.37)
Vd/F (L)	5.39 (23.91)	3.75 (32.41)
Vd/F (L/lb.)	0.08 (18.86)	0.09 (44.03)
*C _{max} (µg/ml)	33.01 (23.51)	29.98 (32.38)
*T _{max} (h)	1.17 (54.90)	0.75 (64.48)

* N = 9

Table 2. Comparison of the PK parameters [Mean (CV%)] of Pseudoephedrine from Children's Advil Cold® Suspension in healthy children and symptomatic children

Study #.	AQ-00-02 (Healthy Subjects)	AQ-00-04 (Symptomatic Children)
N	28	7
Age Range (years)	6-11	2-5
Study Design	Crossover	Parallel
Single Dose (mg)	30	15
AUC _{inf} (ng.h/ml)	1735.21 (26.85)	1291.57 (40.67)
AUC ₀₋₁₂ (ng.h/ml)	1394.07 (24.92)	1004.87 (30.70)
*AUC ₀₋₉ (ng.h/ml)	1206.88 (24.13)	889.70 (26.03)
CL/F (L/h)	18.58 (28.04)	13.80 (47.07)
CL/F L/h*lb.)	0.27 (19.48)	0.31 (33.95)
T _{1/2} (h)	3.90 (8.70)	4.67 (34.51)
Vd/F (L)	105.20 (32.46)	81.17 (16.73)
Vd/F (L/lb.)	1.53 (19.29)	1.90 (21.28)
*C _{max} (ng/ml)	218.29 (23.80)	179.44 (17.07)
*T _{max} (h)	1.87 (43.02)	1.21 (68.75)

*N = 9

The data shown in Tables 1 and 2 above indicate that the mean values for ibuprofen and pseudoephedrine, for AUC, and Cmax (after dose normalization) and, the CL/F and Vd/F values (after adjusting for weight) following single dose administration of Children's Advil® Cold Suspension were somewhat higher in the symptomatic children (aged 2-5) than the healthy children (aged 6-11). However, if one considers the imbalance in the number of subjects, the difference in the design of the study, and the variability associated with the PK parameters, these differences are probably minimal.

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% for the symptomatic children aged 2-5 years old and the healthy children aged 6-11 years old following the administration of _____ are reproduced in Table 3 below:

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

Type of Variability/PK Parameters	Symptomatic Children Aged 2-5 (Study # AQ-00-04 Parallel study) (CV%)		Healthy Children Aged 6-11 (Study # AQ-00-02 Crossover study) (CV%)	
	Ibuprofen	Pseudoephedrine	Ibuprofen	Pseudoephedrine
Intra-subject				
AUC inf			12.0	15.2
AUC t	NA	NA	11.3	15.8
Cmax			14.6	11.6
Inter-subject				
AUC inf	17.83	40.67	25.16	26.85
AUC t	18.10	30.70	25.15	27.67
Cmax	32.38	17.07	23.51	23.80
CL/F	29.89	33.95	18.99	19.48
Vd/F	44.03	21.28	18.86	19.29

The intra-subject variability was less than 20% for both ibuprofen and pseudoephedrine in the healthy children. Inter-subject variability of the PK parameters for ibuprofen (except for AUC) and pseudoephedrine (except for Cmax) was higher in the symptomatic children than the healthy children. The possible sources of increased variability in the symptomatic children include the use of a parallel study design in a multi-center setting.

4.3 Intrinsic Factors

What intrinsic factors influence exposure?

Age:

Primary Analysis (Between-Study): The applicant conducted a between study comparison of data obtained from study # AQ-99-04 in symptomatic children aged 2-5 years and study #AQ-99-02 in healthy children aged 6-12years. Reproduced in Tables 4 and 5 below are summaries of the results:

Table 4: Comparison of Ibuprofen PK Parameters from the Combination Suspension in Symptomatic Children Aged 2 -5 years old Compared with Healthy Children Aged 6-11 years old [Mean (CV%)]

Age Group	*AUC 0-9 (mcg.hr/mL)	AUC 0-12 (mcg.hr/mL)	AUC inf (mcg.hr/mL)	*Cmax (mcg.hr/mL)	CL (L/h/lbs.)
6-11 years (A)* (N=28)	48.01 (24.40)	48.84 (25.15)	49.31 (25.16)	33.01 (23.51)	0.03 (18.99)
2-5 years (B) (N=7)	72.70 (22.48)	68.40 (18.10)	69.44 (17.83)	29.98 (32.38)	0.04 (29.89)
(B/A) % ^b	122.75	115.55	116.42	72.12	96.88

*Reference Group, *N = 9; ^bMean Ratios were based on the least-squares for Ln AUC, Ln Cmax and CL. Only AUC was dose-normalized before comparison.

The data in Table 4 above indicate that the estimated least square means of the pharmacokinetic parameters for ibuprofen in the 2-5 year-old age group were within $\pm 30\%$ of the corresponding estimated least square mean of the pharmacokinetic parameters for the 6-11 year-old age group.

Table 5: Comparison of Pseudoephedrine PK Parameters from the Combination Suspension in Symptomatic Children Aged 2 -5 years old Compared with Healthy Children Aged 6-11 years old [Mean (CV%)]

Age Group	AUC 0-9 (mcg.hr/mL)	AUC 0-12 (mcg.hr/mL)	AUC inf (mcg.hr/mL)	Cmax (mcg.hr/mL)	CL (L/h/lbs.)
6-11 years (A)* (N=28)	603.44 (24.13)	697.04 (24.92)	867.61 (26.85)	218.29 (23.80)	0.273 (19.48)
2-5 years (B) (N=7)	889.70 (26.03)	1004.87 (30.70)	1291.57 (40.67)	179.44 (17.07)	0.308 (33.95)
(B/A) % ^b	113.21	109.64	106.84	66.00	106.08

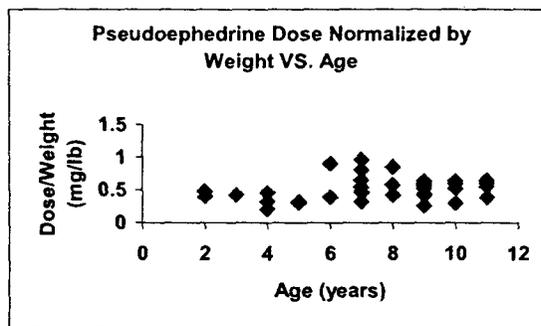
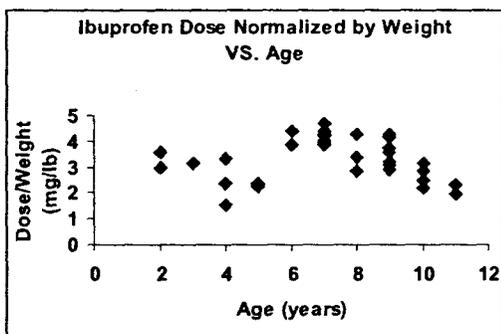
*Reference Group; *N = 9; ^bMean Ratios were based on the least-squares for Ln AUC, Ln Cmax and CL. Only AUC was dose-normalized before comparison.

The data in Table 5 above indicate that the estimated least square mean of the pharmacokinetic parameters for pseudoephedrine in the 2-5 year-old age group were within $\pm 35\%$ of the corresponding estimated least square of the mean pharmacokinetic parameter for the 6-11 year-old age group.

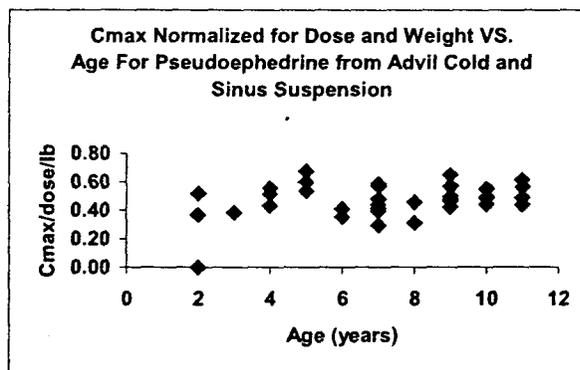
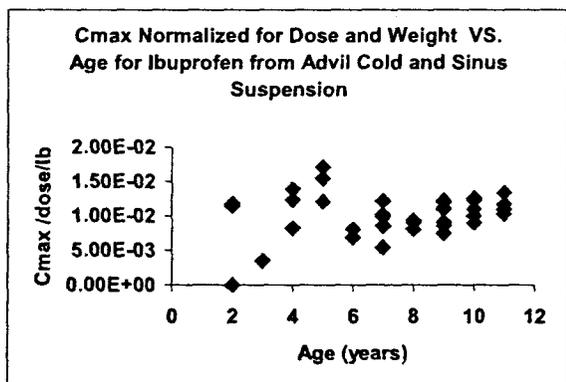
A range of $\pm 35\%$ (previously proposed by the applicant and agreed upon with the FDA, at the Pre-NDA teleconference held on 01/30/01) to declare similarity of the pharmacokinetic parameters (AUC, Cmax and CL) between age groups was used to evaluate the data. Specifically, a parameter would be considered similar if the estimated mean value for the PK parameter from study # AQ-00-04 was within 35% of the estimated mean for those from the reference (i.e. study AQ-99-02). This was based on the following considerations: 1) A CV % of 33% was observed in a previous study (AQ-99-01 tablet formulation for ages 6-11), 2) additional variation might be contributed from comparing results across protocols with different designs and population and, 3) including subjects who did not provide all the required samples in study # AQ-99-04. Therefore based on the aforementioned, the cross comparison indicates that the rate and extent of absorption and, the clearance were similar across the age groups.

C_{max} Evaluation: This reviewer however does not fully agree with the applicant's method of analysis with regards to their evaluation of C_{max} because the applicant did not dose-normalize the data before comparison. Dose-normalization of the C_{max} by dividing the value for the 6-11 years old by 2 results in the C_{max} being higher (~45% for ibuprofen and 35% for pseudoephedrine) in the 2-5 years old age group. However, there was an overlap in the weight of the subjects between the two age groups. In the 2-5 year old age group the mean weight = 41.2 lbs. (range = 27-72 lbs.) and for the 6-11 year old age group the mean weight = 69.36 lbs. (range = 47-113 lbs.).

A graphical representation of the dose normalized by weight versus age is reproduced below:



The graph above shows that if the weight is taken into consideration the dose given to the 2-5 year olds is about the same as that given to the 6-11 year old (especially the 9-11 year old) for ibuprofen and pseudoephedrine. Therefore the difference in C_{max} between the age groups due to differences in the dose administered would be minimal. This is shown in the graphical representations of the C_{max} normalized for dose and weight versus age for ibuprofen and pseudoephedrine from Advil Cold and Sinus reproduced below:



For ibuprofen it appears there were three patients, a 4 year old (weight = 72 lbs.) and two 5 year old's (weight = 47 and 46 lbs.) with slightly higher C_{max} than that obtained in the 6-11 year old group. However, if one takes the imbalance in the data sample size and other sources of variability into account, any differences will be minimal. For pseudoephedrine the data in the graphs above do not suggest a trend in the C_{max} between age groups. A preliminary evaluation of the adverse event profile for study AQ-00-04 indicated that there were only three AE's experienced with the 2-5 year old, and only one of them (rhinitis) was stated by the applicant as

being possibly related to the drug product. From discussions with the medical reviewer (Dr. L. Hu), I was informed that the adverse event profile from the safety study AQ-99-03 did not indicate any safety concern for the drug product. Therefore, the slightly higher Cmax values in the children aged 2-5 years old is unlikely to be clinically relevant.

Gender: There was no significant gender ($p \geq 0.280$) and treatment-by-gender effect ($p \geq 0.113$) observed for the pharmacokinetic parameters AUC and Cmax of Ibuprofen and Pseudoephedrine.

Race: In study AQ-99-02, only 1 patient of the 28 patients was not Caucasian. In study AQ-99-04, there were 9 Black patients, 1 Hispanic, and 1 Asian. Since this was a parallel study the numbers in each group were insufficient to conduct any meaningful analysis.

Weight: In a secondary analysis using data from the healthy children where median weight within gender was used to classify two weight groups in healthy children for ibuprofen and pseudoephedrine, weight group alone was statistically significant ($p < 0.05$) indicating a difference in the weight distribution between the two age groups (<9 and >9). However, treatment by weight group was not statistically significant ($p > 0.138$) suggesting that the differences in weight distribution had no effect on the treatments (i.e. combination vs. single ingredient product).

What is the impact of any differences in exposure in these subgroups on the pharmacodynamics of ibuprofen and pseudoephedrine?

In study AQ-99-04 the major symptoms and the number of children with each symptom were as follows: runny nose 19 (82.6%); sneezing 15 (65.2%); wet cough (phlegm) 12 (52.2%); nasal congestion 11 (47.8%); sore throat 11 (47.8%); headache 7 (30.4%). There was only one child with fever, therefore an assessment of the effect of age on the antipyretic effect could not be carried out with this study. However, the applicant included an article entitled "Effect of age on Ibuprofen pharmacokinetics and antipyretic response"[Kauffman RE, Nelson MV. Effect of age on ibuprofen pharmacokinetics and antipyretic response. J Pediatr 1992; 121:969-973] in which the effect of age on ibuprofen pharmacokinetics was studied in 49 infants and children aged 3 months to 10.4 years. The children included in the study had an acute inter-current febrile illness and axillary temperature of $\geq 38.5^{\circ}\text{C}$. The relationship of plasma concentration to antipyretic effect was examined in 38 of the children. The authors found no correlation between age and any of the pharmacokinetic variables (C_{max} , t_{max} , $t_{1/2\text{abs}}$, $t_{1/2\text{elim}}$, and AUC) for ibuprofen across an age range of 3 months to 10 years. This observation was consistent with the results of the pharmacokinetic studies included in this submission with regards to effect of age on the rate and extent of absorption.

In contrast there was a significant age effect on antipyretic response in terms of the time to onset, percentage change in temperature and area under the percentage vs. time curve. The mean time to onset of antipyresis was 69 minutes in the 14 youngest children (≤ 1 year), and 109 minutes in the 14 oldest children (≥ 6 years old). Also the mean maximum decrease in temperature from baseline was 2.8°C in the youngest age group and 1.8°C in the oldest children. Therefore the results suggested that the younger children had a significantly greater antipyretic response than the older children did.

The authors stated that the absence of an age effect on the pharmacokinetics of ibuprofen indicates that age-related difference in antipyretic response must be due to mechanisms other than an age-related difference in drug concentration. This literature data further supports the data obtained in the between comparison assessment conducted by the applicant that demonstrated that age does not influence the pharmacokinetics of ibuprofen in children.

4.4 Extrinsic Factors

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

Age Group 6-11:

The data demonstrated that the rate and extent of absorption of ibuprofen or pseudoephedrine hydrochloride is not affected by the presence of either one when administered in combination as the suspension to healthy children aged 6-11 years old. Reproduced in the table below is a summary of the pharmacokinetic parameters and 90% confidence intervals for ibuprofen and pseudoephedrine from the combination product and single ingredient products:

Table 6. Ibuprofen Pharmacokinetic Parameters and 90% CI in Healthy Children Aged 6-11 years old

Parameter	Mean (CV%) (N = 28)			
	Children's Advil Cold Suspension (Treatment A)	Children's Advil Oral Suspension (Treatment B)	Ratio of A/B*(%)	90 % Confidence Interval of Ratio
AUClast (mcg.h/mL)	97.69 (25.15)	95.95 (33.45)	104.15	98.83-109.76
AUCinf (mcg.h/mL)	98.63 (25.16)	98.07 (35.78)	103.31	97.75-109.18
Cmax (mcg/mL)	33.01 (23.51)	34.17 (24.95)	98.37	91.97-105.22
Tmax (h)	1.17 (54.90)	1.39 (45.70)		

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

Table 7. Pseudoephedrine Pharmacokinetic Parameters and 90% CI in Healthy Children Aged 6-11 years old

Parameter	Mean (CV%) (N = 28)			
	Children's Advil Cold Suspension (Treatment A)	Children's Sudafed Nasal decongestant Liquid Medication (Treatment B)	Ratio of A/B*(%)	90 % Confidence Interval For Ratio
AUClast (ng.h/mL)	1693.98 (27.67)	1722.07 (31.41)	98.64	91.76-106.05
AUCinf (ng.h/mL)	1735.21 (26.85)	1766.87 (31.36)	98.67	92.03-105.80
Cmax (ng/mL)	218.29 (23.80)	215.14 (23.00)	101.13	95.90-106.65
Tmax (h)	1.87 (43.02)	1.80 (42.13)		

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

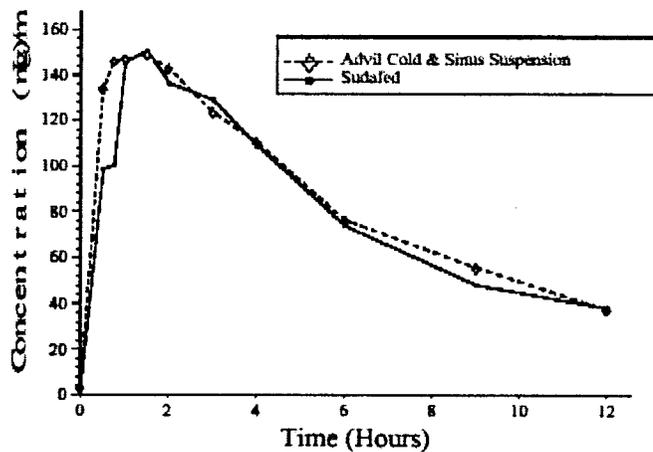
The results as shown in the table above indicate that the 90% CI for Cmax and AUC were within the acceptable limits for bioequivalence (i.e. 80-125%) for ibuprofen and

pseudoephedrine. Therefore the results of this study in children aged 6 - 11 years demonstrated that the presence of pseudoephedrine hydrochloride does not affect the rate and extent of absorption of ibuprofen and vice-versa, when both are administered as a combination suspension.

Age group 2-5:

The applicant conducted a pharmacokinetic drug interaction study in the 2-5 year old age group using the combination product and a single ingredient pseudoephedrine drug product, agreed upon with the FDA at a Pre-IND meeting (held on November 9th, 1999). This is because in the literature it is reported that the terminal elimination half-life value of pseudoephedrine is shorter and the clearance rate faster in children than in adults. Therefore it was expected that an interaction would more likely be seen with pseudoephedrine. In a publication included by the applicant the reported mean terminal half-life value was 3.1 ± 0.5 hrs (pH 6.5) in children (aged 6-12 years old) with seasonal allergic rhinitis. In healthy adults the half-life values of pseudoephedrine reported were 3-6 hours (acidic urine), 5-8 hours (pH 5.8) and 9-16 hrs (alkaline pH) [Simons FER, Gu X, Watson WTA, Simons KJ. Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. J Pediatr 1996;129:729-734]. Inserted below is the graphical representation of the mean plasma concentration of pseudoephedrine versus time that suggests similarity in the mean plasma concentration profile for pseudoephedrine from the combination suspension and the single ingredient product.

Figure 2. AQ-00-04 Mean Pseudoephedrine Hydrochloride (ng/mL) Plasma Concentrations Over Time in Symptomatic Children Aged 2 to <6 Years - Linear Scale



Reproduced in the table below is a summary of the pharmacokinetic parameters for pseudoephedrine from the combination product and single ingredient product:

Table 8. Pseudoephedrine Pharmacokinetic Parameters and Least Squares Ratio in Symptomatic Children Aged 2-5 years old

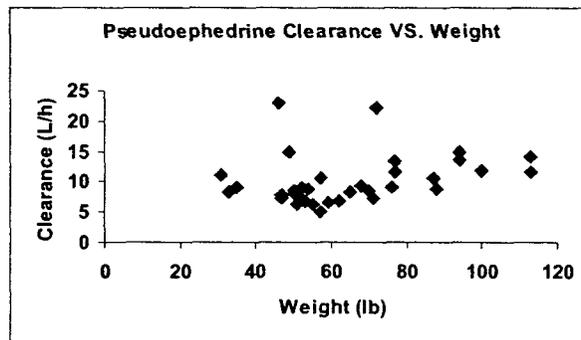
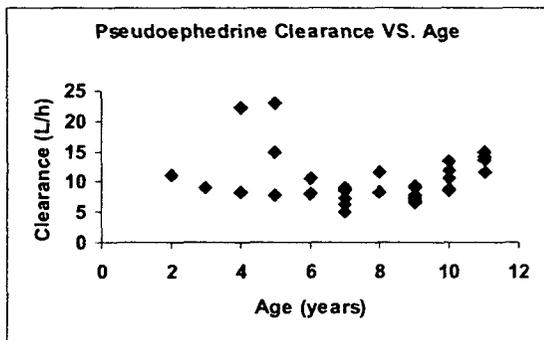
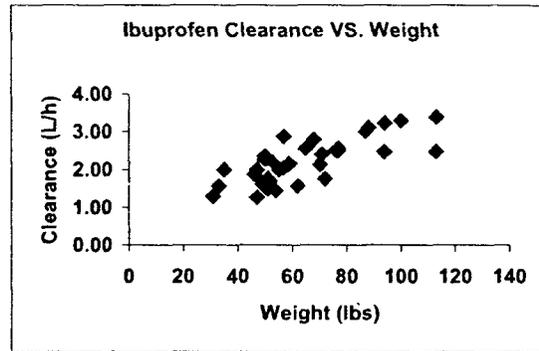
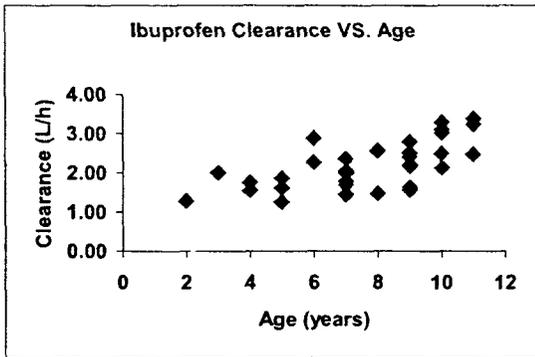
Parameter	Mean (CV%) (N = 9)		
	Children's Advil Cold Suspension (Treatment A)	Children's Sudafed Nasal decongestant Liquid Medication (Treatment B)	Ratio of A/B*(%)
AUC (0-9) (mcg.h/mL)	889.70 (26.03)	849.09 (28.19)	121.95
¹ AUC (0-12) (mcg.h/mL)	1004.87 (30.70)	1015.99 (30.46)	123.67
¹ AUCinf (mcg.hr/mL)	1291.57 (40.67)	1355.38 (40.98)	114.96
Cmax (mcg/mL)	179.44 (17.07)	166.50 (27.33)	123.76
Tmax (h)	1.21 (68.75)	1.46 (47.41)	

*Ratio of least squares means of log transformed values of Treatment A and B; ¹(N = 7)

The data in Table 8 above demonstrates that the estimated mean of the parameters from the combination suspension were within 25% of the corresponding estimated mean parameter for the single ingredient suspension. A range of $\pm 30\%$ (previously proposed by the applicant and agreed upon with the FDA, at a Pre-NDA teleconference held on 01/30/01) to declare similarity of the pharmacokinetic profile of pseudoephedrine hydrochloride in the suspension and the reference standard used. Therefore based on the aforementioned, the data showed that the rate and extent of absorption of pseudoephedrine hydrochloride when administered as a combination suspension is similar to that of pseudoephedrine hydrochloride when administered alone to children aged 2-5 years old.

What other issues are related to dose and dosing regimens?

The applicant has proposed a dosing regimen based on weight and age with a recommendation stated in the label as follows: "If possible use weight to dose; otherwise use age", therefore this suggests a preference for weight based dosing. This was based on the advice of the Nonprescription Drugs Advisory Committee (NDAC) at a meeting held on September 18th, 1997 to discuss labeling and dosing of OTC pediatric analgesic/antipyretic drugs. By consensus, NDAC recommended that weight should be the preferred basis for dosing, if it is known, but that age ranges should also be given for those whose weight is not known. The proposed recommended dose for ibuprofen in the combination suspension is based on the clinically effective dose of ibuprofen, ranging from 5-10 mg/kg, to be repeated every 6 hours if needed, but not to exceed 4 times (40 mg/kg) in 24 hours. In order to evaluate the proposed dosing regimen based on the pharmacokinetics, scatter plots of clearance versus age and weight for ibuprofen and pseudoephedrine from the combination suspension are reproduced below:



The graphs above indicate that although there were a few outliers present in each figure, the scatter indicated that for ibuprofen, it appears that clearance increases with age and weight. However, for pseudoephedrine it appears that there is consistency across age with higher variability in the lower age and weight children group. This finding could also be a function of the smaller sample size in the lower age group. An evaluation of the clearance normalized by weight versus age using a linear regression analysis is reproduced in the Table below (Scatter plots and the linear regression results are attached in the Appendix Pages 31 and 32):

Table 9: Linear Regression Analysis of Ibuprofen and Pseudoephedrine Clearance versus Age from the Combination Suspension

Compound/PK Parameter (N = 35)	Slope (standard error)	Slope p-value	R	Intercept
Ibuprofen	-0.00156 (0.0005)	0.0038	0.476	0.04770
Pseudoephedrine	-0.249 (0.00443)	0.0000	0.670	0.36300

For both ibuprofen and pseudoephedrine the slope of the linear regression of the CL with age was significant as indicated by the p-value in the Table above suggesting that, CL decreases with age. Also the R-values suggest some linear association. However due to the imbalance in the sample size between the two age groups (N=7 (2-5 year olds) and 28 (6-11 year old)), these results are only suggestive, although they do support the proposed dosing regimen in that the dose/lb. (proposed by the applicant decreases with age).

4.5 General Biopharmaceutics

What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The clinical studies (AQ-99-02, AQ-99-03 and AQ-00-04) supporting the suspension product utilized a formulation containing ibuprofen 110 mg / 5 ml and pseudoephedrine HCl 15 mg / 5 ml (Batch No.WH-0846-0001, Batch Size ———. This strength of 110 mg was chosen based on the concern of the mg/kg dosage in the age groups of 11 years and 4-5 years being slightly below 5 mg/kg (discussed at a Pre-IND meeting held on 11/09/99). In subsequent discussions with the agency (letter dated April 17th, 2000 sent by FDA to Whitehall-Robins Healthcare), the applicant was notified of the FDA's recommendation of keeping the strength of ibuprofen at 100 mg/5 ml for the combination to be consistent with the currently marketed strength. It was also communicated that the pharmacokinetic and safety studies obtained from the studies initiated using the clinical combination formulation was considered acceptable for extrapolation to a 100 mg/15mg per 5 mL suspension. Based on this communication the applicant did not conduct a bioequivalence study between the two products. However, the applicant submitted a secondary analysis of the pharmacokinetic data of ibuprofen AUC and Cmax normalized for the 100 mg/5mL dose (Dose normalization for all the other parameters was done by the reviewer), a comparative composition statement, and comparative dissolution data. The results of the dose normalization data are reproduced in the Table below:

Table 10: Summary of the Comparison of the PK parameters (Mean (CV%)) of Ibuprofen from the 110 mg/5mL and the 100 mg/5 mL

Study #.	AQ-00-02 (Healthy Children aged 6-11 years old, N = 28)		AQ-00-04 (Symptomatic Children aged 2-5 years old, N = 9)	
	220	200	110	100
Single Dose (mg)	220	200	110	100
AUC _{inf} (µg.h/ml)	98.63 (25.16)	89.66 (25.16)	69.44 (17.44)	63.13 (17.44)
AUC ₀₋₁₂ (µg.h/ml)	97.69 (25.15)	88.81 (25.15)	68.40 (18.10)	62.18 (18.10)
AUC ₀₋₉ (µg.h/ml)	96.02 (24.40)	87.29 (24.40)	72.70 (22.48)	66.09 (22.48)
Cmax (µg/ml)	33.01 (23.51)	30.01 (23.51)	29.98 (32.38)	27.25 (32.38)

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 applicant did not include data on studies conducted to assess the effect of food on ——— in this submission. However, the proposed draft label states "give with food or milk if stomach upset occurs". For the currently marketed Advil[®] Cold and Sinus Caplets (NDA 19-771, approved in 1989) that consists of Ibuprofen 200mg/pseudoephedrine HCl 30mg, the applicant submitted an in vivo food effect study report (01/26/1997) to fulfill one of their Phase 4 commitments and support their approved labeling "Take with food or milk if occasional mild heartburn, upset stomach or stomach pain occurs with use". Dr. D. Wang reviewed this report and her conclusion was that food does not significantly affect the absorption of Advil Cold and Sinus Caplets and, that this study supported their approved labeling. Since Advil Cold and Sinus Liquid suspension is a more solubilized dosage

form than the caplet, an effect on the absorption in the fed state is unlikely to occur either. Therefore, the results from the food effect study with the caplets can also be applied to support the proposed labeling for the combination suspension.

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

The dissolution method used for the _____ is reproduced below:

Table 11: Dissolution Method and Specifications

Apparatus	USP Apparatus II (paddles)
Speed	50 rpm
Media	900 mL 50mM phosphate buffer, pH 7.2
Sampling Time Points	5, 7.5 and 10 minutes
Number of Units	6 or 12, 5 ml aliquots
Method of Analysis	
Specification	_____

The proposed dissolution method in terms of the apparatus, speed and media is the same as the current dissolution method used by the applicant for Children's Advil Suspension (NDA 20-589, Annual Report 08/27/97). The sampling times (5,10,15,20,30,45,and 60 minutes) and specifications _____ for the ibuprofen suspension alone are however different.

Table 11: Dissolution Results

	Mean Percent Dissolved (SD) N = 12 (Time in Minutes)			
	Ibuprofen-Pseudoephedrine HCl Clinical Study Formulation (WH-0846-0001-001)		Ibuprofen-Pseudoephedrine HCl Proposed Market Formulation (WH-0830-0002-002)	
Time (minutes)	Ibuprofen	Pseudoephedrine HCl	Ibuprofen	Pseudoephedrine HCl
5	/			
7.5	/			
10	/			

The results as shown in the table above demonstrate that for both the product formulations evaluated, _____ Both formulations passed the applicant's dissolution specifications of _____. Also the data indicate that the dissolution profiles for the clinical study formulation and the to-be-marketed formulation are very similar. However, It appears that a tighter specification of _____ would be preferable for ensuring lot-to-lot quality of the drug product.

4.6 Analytical

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

For ibuprofen identification was by

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

Yes the method validation results (see details in table below) demonstrate that the analytical method used for the quantitative determination of ibuprofen and pseudoephedrine in human plasma were reliable and reproducible for the intended use.

Table 12: Analytical Validation Results

Compound		Ibuprofen	Pseudoephedrine
Accuracy	<i>Within-Day</i>		
	<i>Between-Day</i>		
Precision (CV%)	<i>Within-Day</i>		
	<i>Between-Day</i>		
Standard curve range			
Sensitivity (LOQ)			
Selectivity		No interfering endogenous peaks at the retention times of ibuprofen and the internal standard.	No interfering endogenous peaks at the retention times of pseudoephedrine and the internal standard
Stability		Storage @ Room temperature _____ prior to and, after _____ cycles _____ degradation was obtained.	Storage @ Room temperature _____ hours prior to extraction and after _____ cycles _____ degradation was obtained.

**Number of Pages
Redacted** 3



Draft Labeling
(not releasable)

5.2. Individual Study Reviews

5.2.1 NDA 21-373 (Synopsis of Study #AQ-99-02)

Title of Study: A Single-Dose, Randomized, Open-Label, Single Center, Three-Way Crossover Pharmacokinetic Study of Children's Advil® Cold & Sinus Suspension in 6 to <12 Year Old Children

Investigator:

Study Centers:

e
1

Study Period: April 7, 2000 — June 18, 2000

Phase of Development: Phase II

Objectives: To characterize the rate and extent of absorption, distribution, elimination of ibuprofen and pseudoephedrine hydrochloride in children aged 6 to <12 years following a single dose administration of a combination suspension product containing ibuprofen mg/pseudoephedrine hydrochloride 15 mg/5 mL (Children's Cold & Sinus Suspension; Treatment A), a single ingredient containing pseudoephedrine hydrochloride 15 mg/5 mL (Children's Sudafed® Nasal Decongestant Liquid; Treatment B), or a single ingredient product containing ibuprofen 100 mg/5 mL (Children's Advil Oral Suspension; Treatment C).

Study design: Single-Dose, Randomized, Open-Label, Single Center, Three-Way Crossover Pharmacokinetic Study

Study population: Thirty-one healthy children were enrolled however, twenty-eight (13 males and 15 females) completed the study. All but one classified, as "Other" were Caucasian (96%). The average age was 8.6 years, ranging from: 6 to 11 years. Twelve subjects (43%) were aged 6 to 8 years. The average weight and height were 69.4 pounds (ranging from 47 to 113 pounds) and 52.5 inches (ranging from 46 to 59 inches), respectively. The average oral temperature for the subjects was 98.89°F

Age (years old)	Number of Subjects	% of Total	Cumulative %	No. of Male	No. of Female
6	2	7.14	7.14	2	0.0
7	7	25.00	32.14	4	3
8	3	10.71	42.85	1	2
9	7	25.00	67.85	3	4
10	5	17.86	85.71	1	4
11	4	14.29	100	2	2
Total	28	100		13	15

Two subjects (Subjects 001 and 062) were discontinued prior to dosing and were excluded from the safety and pharmacokinetic analyses. Subject 062 was deemed ineligible for the study prior to receiving any study medication due to using a topical cream the day before dosing. One subject (Subject 009) missed two consecutive blood samples and was discontinued from the study after Period II as a protocol violator. This subject was excluded from the pharmacokinetic analyses, but was included in the analysis of safety.

Treatments: Each child received one of the following treatments during each of three treatment periods:

Treatment A. = 10 mLs of _____ whitehall-Robins Healthcare Batch No. WH-0846-0001-001), **Treatment B.** = 10 mLs of Children's Sudafed Nasal Decongestant Liquid Medication (pseudoephedrine hydrochloride 15 mg/5 mL; Warner-Lambert Consumer Healthcare Lot No. 72699L), **Treatment C.** = 11 mLs of Children's Advil® Oral Suspension (ibuprofen 100 mg/5 mL; Whitehall-Robins Healthcare, Lot No. 99267). Each treatment period was separated by no less than 5 days and no more than 14 days.

Subjects were required to fast from 10:00 PM until they were served a standardized breakfast consisting of Cereal-Cheerios®, Milk 2% and 1 Pop Tart, at 6:30 AM the following morning. At approximately 8:00 AM, subjects ingested study drug orally followed by 20 mL water used to rinse the dosing cup. Subjects were allowed only clear liquids such as non-caffeinated beverages or fruit juice beginning 2 hours after dosing. Additional food and liquids were provided at lunch after the 4-hour blood draw. Subjects were discharged 24 hours after dosing.

Pharmacokinetic Sampling:

Blood samples (3 mL for Treatment A and 2 mL for Treatments B and C) for the analysis of racemic ibuprofen and pseudoephedrine hydrochloride levels were collected via

_____) at: pre-dosing (0), and 30, 45, 60, 75, 90 minutes, and 2, 3, 4, 6, 9, 12, and 24 hours after dosing with Treatment A, B and C), except that a 24 hour sample was not collected following Treatment C (Ibuprofen alone). A total of approximately 100 mL of blood was drawn from each subject over the three treatment periods for ibuprofen and pseudoephedrine hydrochloride assays (excluding the two blood samples required for the pre- and post-study clinical laboratory evaluations).

After collection, the blood was centrifuged at _____ The plasma was removed using _____ and each sample was divided into _____ and transferred to polypropylene screw-cap tubes. The plasma samples were stored at _____ until assayed for racemic ibuprofen and pseudoephedrine hydrochloride.

Analytical Methods:

m

Pharmacokinetic and Statistical Analysis:

_____ Log-transformed values of AUCL, AUCI (0-infinity), and Cmax were the primary pharmacokinetic parameters. They were analyzed for differences between treatments using an analysis of variance with effects for gender, subject (gender), period, treatment, carryover, and treatment-by-gender interaction. A 90% two-sided confidence interval for the relative bioavailability, relative to the reference, based on the least square means (equivalent to two one-sided t-tests) was calculated for AUCI, AUCL, and Cmax. Bioequivalence was declared if the 90% two-sided confidence interval for the ratio was between 0.8 and 1.25 for log transformed pharmacokinetic. Covariate analysis was performed to assess the effect of age and body weight using ANOVA.

Results:

Figure 1: A/Q-99-02 Mean Ibuprofen Plasma Concentration (Linear Scale) Over Time in 28 Completing Subjects

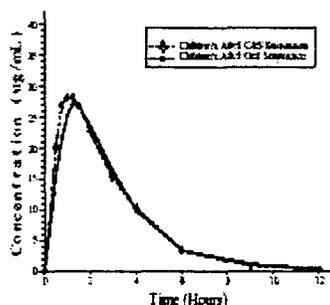


Figure 3: A/Q-99-02 Mean Pseudoephedrine Hydrochloride Plasma Concentration (Linear Scale) Over Time in 28 Completing Subjects

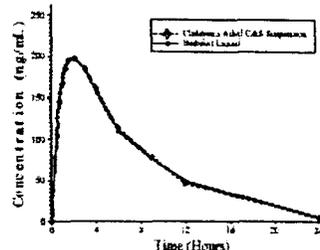


Table 1. Summary of the PK parameters (Mean (CV%)) of Ibuprofen from Children's Advil Cold® Suspension, and Children's Advil® Suspension in healthy children

Drug Product	Children's Advil Cold® Suspension (A)	Children's Advil® Oral Suspension (C)	Ratio of A/C (%)	90% CI
N	28	28	-	
Single Dose (mg)	220	220	-	
AUC _{inf} (µg.h/ml)	98.63 (25.16)	98.07 (35.78)	103.31	97.75-109.18
AUC ₀₋₁₂ (µg.h/ml)	97.69 (25.15)	95.95 (33.45)	104.15	98.83-109.76
Cl/F (L/h)	2.36 (23.60)	2.48 (29.39)	-	-
T _{1/2} (h)	1.60 (13.59)	1.61 (38.64)	-	-
Vd/F (L)	5.39 (23.91)	5.39 (30.45)	-	-
C _{max} (µg/ml)	33.01 (23.51)	34.17 (24.95)	98.37	91.97-105.22
T _{max} (h)	1.17 (54.90)	1.39 (45.70)	-	-

Table 2. Summary of the PK parameters (Mean (CV%)) of Pseudoephedrine from Children's Advil Cold® Suspension, and Sudafed Nasal Decongestant Liquid in healthy children

Drug Product	Children's Advil Cold® Suspension (A)	Sudafed Nasal Decongestant Liquid (B)	Ratio of A/B (%)	90% CI
N	28	28	-	
Single Dose (mg)	30	30	-	
AUC _{inf} (µg.h/ml)	1735.21 (26.85)	1766.87 (31.36)	98.67	93.03-105.80
AUC ₀₋₁₂ (µg.h/ml)	1693.98 (27.67)	1722.07 (31.41)	98.64	91.76-106.05
Cl/F (L/h)	18.58 (28.04)	18.64 (30.56)	-	-
T _{1/2} (h)	3.90 (8.70)	3.98 (11.08)	-	-
Vd/F (L)	105.20 (32.46)	103.6 (29.84)	-	-
C _{max} (µg/ml)	218.29 (23.80)	215.14 (23.00)	101.13	95.90-106.65
T _{max} (h)	1.87 (43.02)	1.80 (42.13)	-	-

Conclusions: Data indicates no PK interaction present because 90% CI of LnAUC and LnC_{max} for IBU and PSE within 80-125%

5.2.2 NDA 21-373 (Synopsis of Study # AQ-00-04)

Title of Study: A Single-Dose, Randomized, Open-Label, Multicenter, Parallel Group Confirmatory Pharmacokinetic Study of Children's Advil® Cold & Sinus Suspension in 2 to <6 year-old Children

Investigators: • _____

Clinical Sites:

Analytical Site: _____

Study Period: July 20, 2000 — February 3, 2001

Phase of Development: Phase II

Objectives: The objective of this study was to obtain pharmacokinetic data on ibuprofen and pseudoephedrine hydrochloride in symptomatic children aged 2 to <6 years following a single dose administration of ibuprofen 110 mg/pseudoephedrine 15 mg per 5 mL or pseudoephedrine 15 mg/5 mL alone.

Study design: Single-Dose, Open-Label, Randomized, Multi-Center, Parallel Confirmatory Pharmacokinetic Study

Study population: The protocol required approximately 50 subjects to be enrolled to ensure that approximately 40 subjects completed the study. Due to enrollment difficulties, the FDA was consulted on February 8, 2001 to discuss the status of the study. During the teleconference, it was agreed that the current enrollment of 23 subjects was adequate based on the number of 2 and 3 year old subjects (n=10) that were enrolled. The study was stopped and a sample size of 23 subjects was analyzed (11 subjects received _____ and 12 subjects received Children's Sudafed Nasal Decongestant Liquid Medication). A total of 23 symptomatic children presenting with symptoms of an acute upper respiratory tract infection (onset within 7 days prior to dosing) were enrolled and were included in the safety analyses.

The average age, weight, and height of the subjects were 3.5 years (range: 2 to 5 years), 38.8 pounds (range: 25 to 72 pounds), and 40 inches (range: 32 to 48 inches), respectively. There were 14 males (60.9%) and nine females (39.1%). Forty-four percent of the subjects were Caucasian, followed by Black (39%), Hispanic (9%), and Asian (4%) and "other" (4%). Children between 2 to 3 years of age were (45%) in the ibuprofen pseudoephedrine hydrochloride group and 42% in pseudoephedrine hydrochloride alone group. The average oral temperature for the subjects was 97.4°F (ranging from 95.5 to 98.8°F), indicating the children were not febrile.

Age (years old)	No. of Male	No. of Female	Number of Patients	% of Total	Cumulative %
2	6	2	8	34.8	34.8
3	2	0	2	8.7	43.5
4	2	4	6	26.1	69.6
5	4	3	7	30.4	100
Total	14	9	23	100	

Age (years old)	Advil C&S Suspension		Sudafed	
	M	F	M	F
2	2	2	4	0
3	1	0	1	0
4	1	2	1	2
5	2	1	2	2
Total	6	5	8	4

Four subjects were discontinued from the study and were excluded from the pharmacokinetic analysis. Subjects 50001(5) and 50002 (2) withdrew voluntarily from the study after their 6-hour blood draw was obtained. For both subjects, the intravenous line was not working after the 6-hour blood draw and the mother did not want another line placed. Due to a difficult pre-dose blood draw, the Investigator was unable to obtain any post-dosing blood samples from Subject 10004 (2). Due to intravenous line difficulty, the Investigator was unable to obtain blood samples from Subject 30005 (2) for the 2-hour through 12-hour time-points. The remaining 19 subjects, 9 receiving ibuprofen/pseudoephedrine hydrochloride suspension and 10 receiving pseudoephedrine hydrochloride alone, completed the study.

Age (years old)	Total (% of Total)	Advil C&S Suspension		Sudafed	
		M	F	M	F
2	5 (26.3)	1	1	3	0
3	2 (10.5)	1	0	1	0
4	6 (31.6)	1	2	1	2
5	6 (31.6)	2	1	2	1
Total	19	5	4	7	3

Enrolled % of 2-3 years old = 43.5% and Completed = 36.8%.

Treatments: Subjects who had not eaten within 60 minutes prior to dosing and who met all other inclusion/exclusion criteria were administered, via syringe, their single oral dose of one of the following treatments:

Treatment A. = 5 mLs of _____ (ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg/5 mL; Whitehall-Robins Healthcare Batch No. WH-0846-0001-001), **Treatment B.** = 5 mLs of Children's Sudafed® Nasal Decongestant Liquid Medication (pseudoephedrine hydrochloride 15 mg/5 mL; Warner-Lambert Consumer Healthcare Lot No. 72699L). Following dosing, subjects were allowed clear liquids such as non-caffeinated beverages or fruit juice beginning one hour after dosing. Additional food and liquids (e.g. water, non-caffeinated beverages, or fruit juice and bland foods such as saltines, applesauce, graham crackers, and yogurt) were provided after the hour four-blood draw *ad libitum*. Dinner was available at approximately 6:00 PM.

Pharmacokinetic Sampling:

Blood samples (3 mL for Treatment A and 2 mL for Treatment B) for the analysis of racemic ibuprofen and pseudoephedrine hydrochloride levels were collected via _____

at: pre-dosing (0), and 30, 45, 60, 90 minutes, and 2, 3, 4, 6, 9, and 12 hours after dosing. A total of approximately _____ of blood in treatment group A and 22 mL in treatment group B was drawn from each subject for ibuprofen and pseudoephedrine hydrochloride assays (excluding the two blood samples required for the pre- and post-study clinical laboratory evaluations). After collection, the blood was _____. The plasma was removed using disposable pipettes and each sample was divided into _____ and transferred to polypropylene screw-cap tubes. The plasma samples were stored at _____ until assayed for racemic ibuprofen and pseudoephedrine hydrochloride.

Analytical Methods: _____

Pharmacokinetic and Statistical Analysis:

All pharmacokinetic parameters were computed using WinNonlin™ version 2.1 _____ using the plasma concentrations and the sampling times provided by _____. All statistical analyses were performed using SAS version 6.12 (SAS Institute, Cary, NC). The primary pharmacokinetic parameters AUC Cmax and CL were analyzed. The AUC, Cmax and CL (on the log transformed scale) were analyzed for differences between formulations using an analysis of variance with effects for treatment, gender, and body weight. The other pharmacokinetic parameters were summarized. Since there were six subjects missing blood samples at hour 12, it was decided that both AUC0-9 and AUC0-12 would be calculated and analyzed and AUC0-9 would be considered the primary pharmacokinetic parameter. The pharmacokinetic profiles were considered similar if the estimated mean parameter from the combination suspension was within _____ of the corresponding estimated mean parameter for the reference (agreed upon with the FDA). A _____ range (as agreed upon with the FDA) was used to assess the similarity of the pharmacokinetic profile of the suspension in symptomatic children aged 2 to <6 years to healthy children aged 6 to <12 years. This was based on the following considerations: (1) A coefficient of variation of 33% was observed in a previous study of Advil Cold & Sinus tablets in healthy children aged 6 to <12 years, (2) additional variation would arise from comparing results across protocols with different designs (*i.e.*, parallel, multicenter vs. traditional crossover, single center) and different study populations (*i.e.*, symptomatic children aged 2 to <6 years vs. healthy children aged 6 to <12 years); (3) increased variation due to including subjects who did not provide all the required samples.

Results:

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Figure 1. AQ-00-04 Mean Ibuprofen (ug/mL) Plasma Concentrations Over Time in Symptomatic Children Aged 2 to <6 Years – Linear Scale

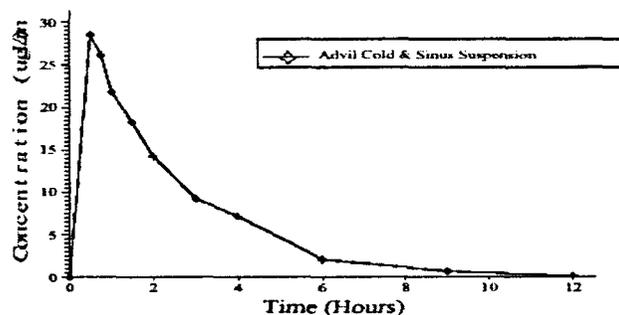


Table 1. Summary of the PK parameters (Mean (CV%)) of Ibuprofen and Pseudoephedrine from Children's Advil Cold® Suspension and Sudafed Nasal decongestant Liquid in symptomatic children

Drug Product	Children's Advil Cold® Suspension	Children's Advil Cold® Suspension (A)	Sudafed Nasal Decongestant Liquid (B)	Ratio of A/B (%) for Pseudoephedrine
Active drug determined	Ibuprofen	Pseudoephedrine	Pseudoephedrine	Pseudoephedrine
N	7	7	7	7
Single Dose (mg)	110	15	15	NA
AUC _{inf} (µg.h/ml)	69.44 (17.83)	1291.57 (40.67)	1355.38 (40.98)	114.96
AUC ₀₋₁₂ (µg.h/ml)	68.40 (18.10)	1004.87 (30.70)	1015.99 (30.46)	123.67
*AUC ₀₋₉ (µg.h/ml)	72.70 (22.48)	889.70 (26.03)	849.09 (28.19)	121.95
Cl/F (L/h)	1.63 (17.15)	13.80 (47.07)	13.12 (47.34)	84.98
T _{1/2} (h)	1.57 (17.37)	4.67 (34.51)	5.25 (35.67)	NA
Vd/F (L)	3.75 (32.41)	81.17 (16.73)	88 (20.39)	NA
*C _{max} (µg/ml)	29.98 (32.38)	179.44 (17.07)	166.50 (27.33)	123.76
*T _{max} (h)	0.75 (64.48)	1.21 (68.75)	1.46 (47.41)	NA

* n=9

Estimated mean of PK parameter from combination product is within \pm of estimated mean of single ingredient suspension.

Conclusions: Pharmacokinetic profile of pseudoephedrine hydrochloride in the combination suspension is similar to that of the single ingredient suspension in symptomatic children aged 2-5 years old.

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5.2.3 Tables of comparison and analysis of PK data between and within studies

Whitehall-Robins Healthcare
Amendment to a Pending Application: Biopharmaceutics
November 14, 2001

NDA 21-373
Children's Advil Cold Suspension
Ibuprofen/Pseudoephedrine HCl
Date: 02NOV01
Time: 10:10

CONFIDENTIAL

Whitehall-Robins Healthcare
PROTOCOL #: AQ-00-04
INVESTIGATOR: Pooled

Children's Advil Cold & Sinus Confirmatory Pharmacokinetic Study

Table F.1

Within-Study Pseudoephedrine Comparison

	Ln AUC9 (ng.h/mL)	Ln AUC12 (ng.h/mL)	Ln AUCI (ng/mL)	Ln Cmax (ng.h/mL)	AUC9 (ng.h/mL)	AUC12 (ng/mL)	AUCI (ng.h/mL)	Cmax (ng.h/mL)	CI (L/h)
CAS Suspension(A)									
Mean *	6.76(860.94)	6.86(951.62)	7.08(1189.89)	5.18(176.82)	889.70	1004.87	1291.57	179.44	13.800
SD	0.28	0.30	0.45	0.19	231.56	388.54	625.22	30.62	6.40
CV%	4.12	4.41	6.48	3.64	26.03	38.78	48.67	17.07	47.07
n	9	9	7	9	9	7	7	9	7
Sudafed(B)									
Mean *	6.71(816.60)	6.79(887.45)	7.13(1250.04)	5.08(160.69)	849.09	1016.99	1356.38	166.50	13.117
SD	1.30	0.33	0.48	0.29	239.36	309.49	655.46	45.50	6.21
CV%	4.46	4.90	6.41	5.83	28.19	30.46	48.98	27.33	47.34
n	10	10	6	10	10	6	6	10	6
Least-Squares Means *, ‡									
CAS Suspension(A)	6.85(942.52)	6.95(1043.38)	7.28(1342.66)	5.25	968.47	1081.24	1427.24	190.79	12.075
Sudafed(B)	6.65(772.90)	6.74(843.67)	7.06(1167.92)	5.03	808.59	966.10	1289.62	159.86	14.210
Ratio of Least-Squares Means **									
(A/B)%	121.95	123.67	114.96	121.78	118.78	111.92	110.67	119.35	84.98

* For log-transformed parameters, the antilog of the mean is reported within parentheses.

** For log transformed parameters, ratio of antilog of least squares means are reported.

‡ Based on the ANOVA model with treatment, gender, and weight effects.

Whitehall-Robins Healthcare
Amendment to a Pending Application: Biopharmaceutics
November 14, 2001

NDA 21-373
Children's Advil Cold Suspension
Ibuprofen/Pseudoephedrine HCl
Date: 02NOV01
Time: 10:11

CONFIDENTIAL

Whitehall-Robins Healthcare
PROTOCOL #: AQ-00-04
INVESTIGATOR: Pooled

Children's Advil Cold & Sinus Confirmatory Pharmacokinetic Study

Table F.2

Between-Study Ibuprofen Comparison

	Ln AUC9 (ug.h/mL)	Ln AUC12 (ug.h/mL)	Ln AUCI (ug/mL)	Ln Cmax (ug.h/mL)	AUC9 (ug.h/mL)	AUC12 (ug/mL)	AUCI (ug.h/mL)	Cmax (ug.h/mL)	CI (L/h)	Adj-Cl (L/h.kg)
AQ-99-02(A)										
Mean *	3.94(48.71)	3.88(47.44)	3.87(47.90)	3.47(22.15)	48.01	48.84	49.31	33.01	2.38	0.83
SD	0.24	0.24	0.24	0.24	11.72	12.29	12.41	7.76	0.58	0.07
CV%	6.10	6.33	6.30	6.78	24.40	25.15	25.16	23.51	21.80	18.99
n	28	28	28	28	28	28	28	28	28	28
AQ-00-04(B)										
Mean *	4.28(71.14)	4.21(67.48)	4.23(68.52)	3.24(28.15)	72.79	88.40	89.44	29.98	1.83	0.84
SD	0.27	0.19	0.18	0.41	18.34	12.38	12.38	9.73	0.29	0.07
CV%	5.16	4.25	4.15	12.27	22.48	18.10	17.88	32.38	17.15	29.89
n	9	7	7	9	9	7	7	9	7	7
Least-Squares Means *, ‡										
AQ-99-02(A)	3.89(48.18)	3.90(48.32)	3.91(49.78)	3.52	50.44	50.72	51.20	34.52	2.27	0.84
AQ-00-04(B)	4.18(80.27)	4.04(58.99)	4.06(57.95)	3.18	64.54	80.17	81.19	25.12	2.02	0.83
Ratio of Least-Squares Means **										
(B/A)%	122.75	115.55	114.42	72.12	127.99	118.88	119.51	72.82	88.86	96.88

* For log-transformed parameters, the antilog of the mean is reported within parentheses.

** For log transformed parameters, ratio of antilog of least squares means are reported.

‡ Based on the ANOVA model with gender, weight, and study effects.

Note: AUC values from study AQ-99-02 were divided by 2 before analysis to account for higher dosing in older age group. Adj-Cl=Cl/weight.

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Whitehall-Robins Healthcare
 Amendment to a Pending Application: Biopharmaceutics
 November 14, 2001

MDA 21-373
 Children's Advil Cold Suspension
 Ibuprofen/Pseudoephedrine HCl
 Date: 02/09/03
 Time: 10:13

CONFIDENTIAL

Whitehall-Robins Healthcare
 PROTOCOL #: AQ-00-04
 INVESTIGATOR: Pooled

Children's Advil Cold & Sinus Confirmatory Pharmacokinetic Study

Table F.3

Between-Study Pseudoephedrine Comparison

	Ln AUC9 (ng.h/mL)	Ln AUC12 (ng.h/mL)	Ln AUC (ng/mL)	Ln Cmax (ng.h/mL)	AUC9 (ng.h/mL)	AUC12 (ng/mL)	AUC (ng.h/mL)	Cmax (ng.h/mL)	CI (L/h)	Adj-CL (L/h.1b)
AQ-99-02(A)										
Mean *	6.37(406.19)	6.52(675.04)	6.73(837.45)	5.36(212.40)	603.44	697.04	867.61	218.29	18.58	0.273
SD	0.25	0.26	0.27	0.24	145.61	173.69	232.94	51.94	5.21	0.053
CVE	3.89	3.93	4.06	4.45	24.13	28.92	26.96	23.80	28.04	19.48
n	28	28	28	28	28	28	28	28	28	28
AQ-00-04(B)										
Mean *	6.76(860.94)	6.87(961.26)	7.03(1109.09)	5.18(176.82)	889.70	1004.97	1291.57	179.44	13.80	0.308
SD	0.28	0.33	0.45	0.19	231.56	308.54	525.22	30.62	6.50	0.104
CVE	4.12	4.80	6.40	3.64	26.03	30.70	40.67	17.07	47.07	33.95
n	9	7	7	4	9	7	7	9	7	7
Least-Squares Means *,§										
AQ-99-02(A)	6.44(623.52)	6.57(710.60)	6.78(884.28)	5.41	640.11	730.09	913.63	229.37	17.65	0.277
AQ-00-04(B)	6.56(785.86)	6.66(779.12)	6.85(944.78)	5.00	770.89	862.17	1093.82	143.95	18.10	0.294
Ratio of Least-Squares Means ** (B/A)§										
	113.21	109.64	106.84	66.80	120.43	117.96	119.72	62.76	103.14	106.06

* For Log-transformed parameters, the antilog of the mean is reported within parentheses.

** For Log transformed parameters, ratio of antilog of least squares means are reported.

§ Based on the ANOVA model with gender, weight, and study effects.

Note: AUC values from study AQ-99-02 were divided by 2 before analysis to account for higher dosing in older age group. Adj-CL=CL/weight.

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5.2.4. Linear regression analysis of clearance versus Age for ibuprofen and pseudoephedrine from the combination suspension

Ibuprofen:

STATISTIX 7.0

3/29/02, 4:19:59

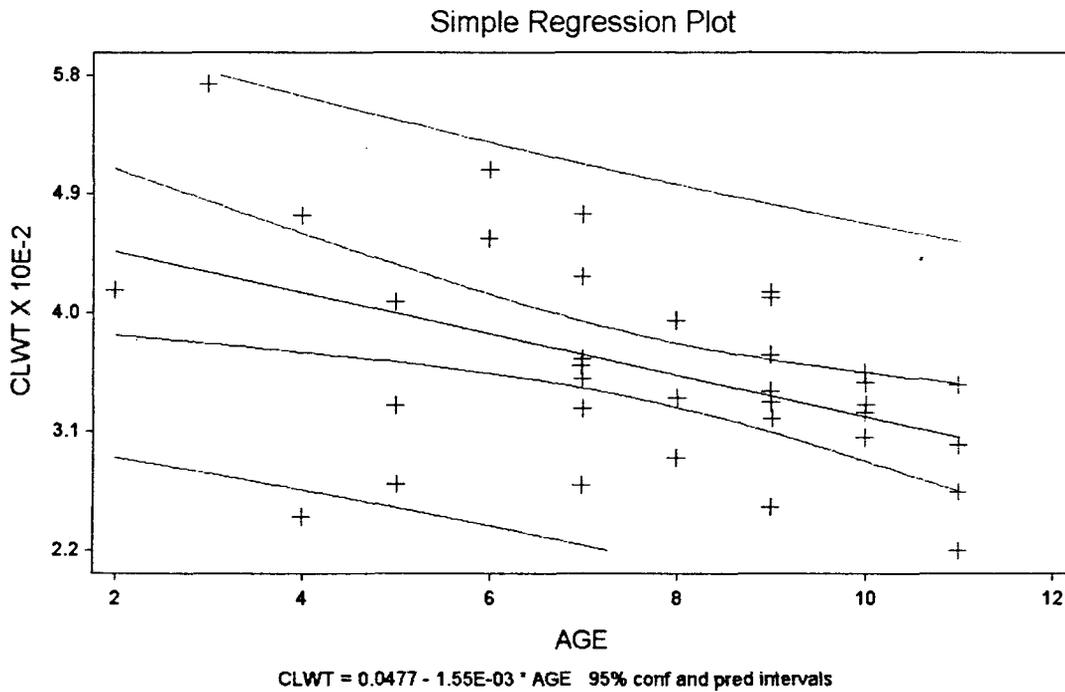
PM

UNWEIGHTED LEAST SQUARES LINEAR REGRESSION OF CLWT

PREDICTOR VARIABLES	COEFFICIENT	STD ERROR	STUDENT'S T	P
CONSTANT	0.04770	0.00403	11.84	0.0000
AGE	-0.00156	4.995E-04	-3.11	0.0038
R-SQUARED	0.2270	RESID. MEAN SQUARE (MSE)	4.869E-05	
ADJUSTED R-SQUARED	0.2036	STANDARD DEVIATION	0.00698	

SOURCE	DF	SS	MS	F	P
REGRESSION	1	4.720E-04	4.720E-04	9.69	0.0038
RESIDUAL	33	0.00161	4.869E-05		
TOTAL	34	0.00208			

CASES INCLUDED 35 MISSING CASES 0



Pseudoephedrine:

STATISTIX 7.0
PM

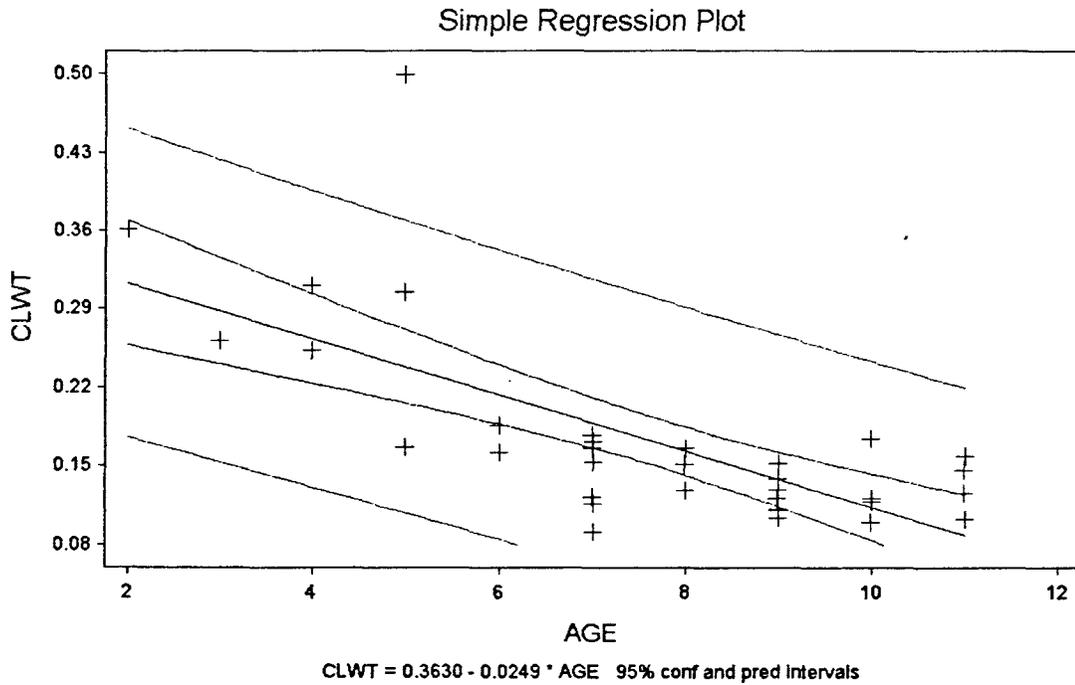
3/29/02, 4:25:05

UNWEIGHTED LEAST SQUARES LINEAR REGRESSION OF CLWT

PREDICTOR VARIABLES	COEFFICIENT	STD ERROR	STUDENT'S T	P
CONSTANT	0.36300	0.03577	10.15	0.0000
AGE	-0.02494	0.00443	-5.63	0.0000
R-SQUARED	0.4895	RESID. MEAN SQUARE (MSE)	0.00384	
ADJUSTED R-SQUARED	0.4741	STANDARD DEVIATION	0.06193	

SOURCE	DF	SS	MS	F	P
REGRESSION	1	0.12138	0.12138	31.65	0.0000
RESIDUAL	33	0.12657	0.00384		
TOTAL	34	0.24795			

CASES INCLUDED 35 MISSING CASES 0



5.3. Cover Sheet and 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	21-373	Brand Name	Children's Advil Cold Suspension	
OCPB Division (I, II, III)	III	Generic Name	Ibuprofen 100mg/5mL and Pseudoephedrine 15 mg/5mL	
Medical Division	HFD-550	Drug Class	Analgesic/Antipyretic and Nasal decongestant	
OCPB Reviewer	Abi Adebawale	Indication(s)	OTC use in temporarily relieving symptoms of the common cold, sinusitis, or flu, headache, nasal congestion, and body aches and pains	
OCPB Team Leader	Dennis Bashaw	Dosage Form	Suspension	
IND Number		Dosing Regimen	1 (for 2-5 yrs) or 2 (for 6-11yrs) teaspoonfuls every 6 hours in children aged 2 to < 12 years old.	
Date of Submission	18 th June, 2001	Route of Administration	Oral	
Estimated Due Date of OCPB Review	18 th February, 2001	Sponsor	Whitehall-Robins Healthcare	
PDUFA Due Date	18 th April, 2001	Priority Classification	6S	
Division Due Date	18 th March, 2001			
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		Children aged 6 to < 12 years old
multiple dose:				
Patients-				
single dose:	X	1		Children aged 2 to < 6 years old
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:				Conducted as a Phase IV Commitment using CoAdvil caplets (NDA 19771)
Dissolution:	X			
(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 <u>not</u> filable (or an attachment if applicable). For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Is the in vivo bioavailability of the combination product equivalent to the in vivo bioavailability of each active ingredient administered as separate single ingredient preparations? If it can be assumed that there is no age effect, is the pharmacokinetics of the combination drug product similar in symptomatic patients and healthy volunteers? What is the pharmacodynamic (PD) effect in terms of temperature reduction of the combination product compared with the single ingredient pseudoephedrine preparation? If a difference in PD is perceived, does this suggest an interaction of pseudoephedrine on Ibuprofen in the combination product?			
Other comments or information not included above				
Primary reviewer Signature and Date	Abi Adebawale (07/17/01)			
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 Adebawale
4/4/02 10:22:28 AM
BIOPHARMACEUTICS

Dennis Bashaw
4/5/02 02:29:44 PM
BIOPHARMACEUTICS

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ON ORIGINAL**