CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-373

MEDICAL REVIEW(S)

NDA #:	21-373
Drug Name:	Children's Advil Cold Suspension Ibuprofen 100 mg/pseudoephedrine HCl 15 mg per 5 ml
Sponsor:	Whitehall Robins
Pharmocologic Category:	Pediatric analgesic/antipyretic/nasal decongestant
Proposed Indications:	For temporary relief of symptoms associated with common cold, sinusitis, or flu, including nasal congestion, headache, fever, body aches and pains; in children 2 to <12 years
Submission:	June 15, 2001
Review Date:	March 28, 2002

APPEARS THIS WAY
ON ORIGINAL

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Executive Summary

I. Recommendations

This original NDA is for Children's Advil Cold (ibuprofen 100 mg/pseudoephedrine hydrochloride 15 mg/ 5 mL), a nonprescription drug for the temporary relief of the following cold, sinus and flu symptoms: nasal and sinus congestion, headache, stuffy nose, sore throat, minor aches and pains, and fever. The product is intended for use in children 2 years to under 12 years of age. Ibuprofen has a long history of use, first as a prescription medication since 1969. It was approved as an over-the-counter (OTC) product in 1984 for adults and in 1995 for children. Pseudoephedrine has been marketed as an OTC pediatric nasal decongestant for over 2 decades. The efficacy and safety of pseudoephedrine hydrochloride was recognized by inclusion in the 1994 Final Nasal Decongestant Monograph.

An adult OTC ibuprofen/pseudoephedrine combination product marketed by Whitehall was approved by the FDA in 1989 for adults and children 12 years of age and older. A pediatric ibuprofen/pseudoephedrine suspension product has been marketed OTC by McNeil Consumer Healthcare since 2000.

This NDA is evaluated as approvable.

II. Summary of Clinical Findings

The clinical trials to support approval included in this application are two pharmacokinetic studies, AQ-99-02 (consisting of 29 children 6 to <12 years) and AQ-00-04 (consisting of 23 children <6 years), and a safety study, AQ-99-03 (consisting of 104 children 2 to <12 years). Also reviewed for this application were the results of worldwide post-marketing surveillance, using the FDA Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) databases and the Sponsor's safety database. Most of the reports came from the US and France. In addition, reports from the American Association of Poison Control Centers (AAPCC) and the Drug Abuse Warning Network (DAWN) were reviewed for overdose and abuse potential.

The bioavailability of ibuprofen and pseudoephedrine in this combination product have been shown to be similar to those of the individual components and similar across the age groups studied. The safety study and literature review were supportive of safety. The post-marketing surveillance review did not reveal unexpected adverse events and provided evidence for a low abuse potential. More than 30% of reported adverse events for pediatric combination product were allergic events.

The Sponsor proposed a 3 day limit for fever or pain and a 7 day limit for cold, sinus and flu symptoms. Due to the limited exposure of subjects with fever and subjects who used the drug for 7 days in the safety trial, there is insufficient data to support a 7 day duration of use for children. Thus, approval for a 3 day duration of use is recommended.

Clinical Review

I. Introduction and Background

A. Identity and Indications

The sponsor proposes the name Children's Advil Cold for the combination product ibuprofen with pseudoephedrine HCl in liquid suspension. The formulation consists of ibuprofen 100 mg/pseudoephedrine hydrochloride 15 mg/ 5 mL suspension. The proposed OTC indication is: for the temporary relief of cold, sinus and flu symptoms: nasal and sinus congestion, headache, stuffy nose, sore throat, minor aches and pains, and fever, in children 2 to <12 years. A combination product can be more convenient to administer to children.

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), has a long history of use, first as a prescription medication since 1969 and subsequently as an over-the-counter (OTC) product for adults and children over 12 years of age, since 1984, and for children between 2 and 12 years of age, since 1995. Indications are for the temporary reduction of fever and relief of minor aches and pains due to the common cold, flu, sore throat, headaches and toothaches. Pseudoephedrine, a sympathomimetic amine, has been available as an OTC pediatric nasal decongestant for over 2 decades for the temporary relief of nasal congestion due to the common cold, hay fever, or other respiratory allergies and nasal congestion associated with sinusitis. The efficacy and safety of pseudoephedrine hydrochloride was recognized by inclusion in the Final Nasal Decongestant Monograph in 1994.

The present application includes two pharmacokinetic studies (AQ-99-02 and AQ-00-04) and a safety study (AQ-99-03). The clinical studies included in this NDA were conducted using an ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg/5 mL suspension product. Subsequent to initiation of this clinical program, it was agreed that Whitehall-Robins Healthcare would develop (letter dated April 27, 2000) a formulation for Children's Advil Cold containing ibuprofen 100 mg/ 5 mL. This was done to avoid potential confusion with an available ibuprofen and pseudoephedrine hydrochloride pediatric product for over-the-counter (OTC) use. In addition, FDA acknowledged that data obtained from the pharmacokinetic and safety studies using the ibuprofen 110 mg/ 5 mL formulation were acceptable for extrapolating to an ibuprofen 100 mg/ 5 mL formulation.

B. State of Armamentarium

On August 1, 2000, the FDA approved NDA 21-128 for pediatric ibuprofen/pseudoephedrine combination suspension, which is currently marketed by McNeil Consumer Healthcare.

C. Milestones in Development

The FDA letter of May 30, 2000 was an official Written Request pursuant to Section 505A of the Food Drug and Cosmetic Act. Information from three studies was requested:

- Study 1, a single dose PK study of ibuprofen/pseudoephedrine HCl suspension in healthy children ages 6 through 11 years; study design to be three-way crossover (ibuprofen/pseudoephedrine combination, pseudoephedrine, ibuprofen) with at least 24

completers; primary study objectives were to measure PK parameters of the combination and to assess potential for drug-drug interaction by comparing the combination with components administered individually;

- Study 2, a single dose confirmatory PK study in children ages 2 through 5 years with symptoms of acute upper respiratory infection; a two-arm, randomized, parallel design comparing ibuprofen/pseudoephedrine combination with pseudoephedrine alone; at least 40 completers and at least 20 per arm; primary study objectives were to measure PK parameters of the combination and to assess potential for drug-drug interaction by comparing the combination with pseudoephedrine;
- Study 3, a multiple dose safety study of ibuprofen/pseudoephedrine HCl suspension in at least 75 children ages 2 through 11 years with symptoms of acute upper respiratory infection to be dosed as recommended in the proposed labeling. The primary study objective was to measure safety of repeated administration of ibuprofen/pseudoephedrine combination in the targeted pediatric population

The drug-specific safety concerns as transmitted to the sponsor in the FDA letter of 30 May 2000 were (for all three studies): development of exacerbation of asthma, anaphylactoid reactions, CNS effects, and hemodynamic effects.

D. Foreign experience

The ibuprofen and pseudoephedrine hydrochloride combination has been marketed as a tablet/caplet adult formulation since 1989 (Whitehall-Robins Healthcare approved NDA 19-771). The tablet/caplet formulation is available OTC in the following countries : Aruba, Curacao, Jamaica, Trinidad, Guyana, United Kingdom, Ireland, Canada, and France. Whitehall-Robins is not aware of any withdrawal in any country for any reason related to safety or effectiveness of Advil Cold & Sinus Tablets/Caplets since these products were marketed internationally (see Appendix A for details). The Czech Republic switched pseudoephedrine hydrochloride from OTC to prescription status in 2000, in order to stop diversion of OTC pseudoephedrine to illicit manufacture of methamphetamine, not because of safety concerns with pseudoephedrine itself.

II. Chemistry, Microbiology and Other Clinically Relevant Findings

The proposed drug product is a suspension formulation containing ibuprofen and pseudoephedrine HCl. Chemistry, manufacturing and controls information pertaining to the drug substances and the clinical formulation was provided in [redacted] (February 29, 2000). The clinical studies (AQ-99-02, AQ-99-03 and AQ-00-04) supporting the suspension product utilized a formulation containing ibuprofen [redacted] mg / 5 ml and pseudoephedrine HCl 15 mg / 5 ml. Whitehall-Robins also manufactured [redacted] full-scale stability batches [redacted] rape-flavored [redacted] containing the "original" ibuprofen levels (i.e. [redacted] mg / 5 ml) in support of the NDA submission.

In subsequent discussions with the Agency, it was agreed that the market formulation should contain 100 mg / 5 ml ibuprofen. It was also agreed that the data from the pharmacokinetic and safety studies using the clinical formulation could be extrapolated to support the proposed market formulation. Since the NDA stability batches had already been manufactured using [redacted] Whitehall-Robins proposed to manufacture a [redacted] of additional stability batches at the 100 mg / 5 ml concentration (reference: [redacted] submitted on

May 10, 2000). Based on the similarity between the formulations, the FDA agreed [redacted] additional batch of each flavor at the lower ibuprofen concentration would be required for the NDA, in addition to the [redacted] batches that had already been manufactured and placed on stability (reference: [redacted] - FDA communication dated June 6, 2000). Whitehall-Robins has decided to pursue only the grape-flavored formulation. Consequently, the NDA included only information pertaining to the grape formulation which was used in the pivotal clinical and stability studies. (Refer to Chemistry Review for details.)

For nonclinical pharmacology and toxicology information on ibuprofen/ pseudoephedrine hydrochloride, Whitehall-Robins Healthcare referred to NDA Submission (19-771) dated September 1, 1987 for CoAdvil ® /Advil ® Cold & Sinus Tablets and Caplets (Volume 1.4, Non-Clinical Pharmacology and Toxicology; Overview of Non-Clinical Pharmacology and Toxicology for Ibuprofen, Pseudoephedrine, and Ibuprofen/Pseudoephedrine). Summaries of the following are provided in NDA 19-771: for ibuprofen, mode of action, anti-inflammatory activity, analgesic and antipyretic activity, pharmacology, pharmacokinetics and metabolism, and toxicology; for pseudoephedrine hydrochloride, mode of action, cardiovascular effects, bronchodilatory activity, central nervous system effects, pharmacology, pharmacokinetics and metabolism, and toxicology; for the combination of ibuprofen and pseudoephedrine hydrochloride, an oral toxicity study in mice and rats. (Refer to Pharmacology/Toxicology Review.)

III. Human Pharmacokinetics

Two pharmacokinetic studies were conducted in support of this NDA for an ibuprofen/pseudoephedrine hydrochloride suspension product for use in children aged 2 to <12 years. Study AQ-99-02 compared the ibuprofen/pseudoephedrine hydrochloride suspension to ibuprofen suspension and pseudoephedrine hydrochloride alone in healthy children aged 6 to <12 years. Study AQ-00-04 compared the ibuprofen/pseudoephedrine hydrochloride suspension to pseudoephedrine hydrochloride alone in children aged 2 to <6 years with symptoms of an acute upper respiratory infection.

A. PK study AQ-99-02

Study AQ-99-02 characterized the rate and extent of absorption and the distribution and elimination of ibuprofen and pseudoephedrine hydrochloride in healthy children aged 6 to <12 years. This was a single-dose, randomized, open-label, single center, three-way crossover pharmacokinetic study. The three treatments evaluated were: Children's Advil ® Cold (ibuprofen [redacted] pseudoephedrine hydrochloride 15 mg/5 mL), Children's Sudafed ® Nasal Decongestant Liquid Medication (pseudoephedrine hydrochloride 15 mg/5 mL), and Children's Advil Oral Suspension (ibuprofen 100 mg/5 mL).

Additional information on the pharmacokinetic results can be found in the review by Dr. Adebowale. These results indicate that the rate and extent of absorption of ibuprofen and pseudoephedrine hydrochloride from the combination suspension are similar to those from the individual components, when both are administered alone. The rate and extent of absorption of either component drug is not affected by the presence of the other.

There was only one adverse event in the study. Subject 009 reported dizziness of moderate severity the night before receiving pseudoephedrine in the first treatment phase. The adverse event was unrelated to the treatment since it occurred the night before dosing. No subject

discontinued due to an adverse event. No serious adverse experiences or deaths occurred during the study. No abnormal vital signs were noted. The physical examination and laboratory evaluation results at the end of the study did not reveal any clinically significant findings.

B. PK study AQ-00-04

Study AQ-00-04 was a single-dose, randomized, open-label, parallel group pharmacokinetic study of Children's Advil ® Cold in 2 to <6 year-old children with symptoms of acute upper respiratory infection. This multicenter study compared the subject combination drug (ibuprofen /pseudoephedrine hydrochloride 15 mg/5 mL) with Children's Sudafed ® Nasal Decongestant Liquid Medication (pseudoephedrine hydrochloride 15 mg/5 mL).

Approximately 50 children were to be enrolled to ensure that approximately 40 children completed the study with a representative sampling over the 2 to <6 year age range and gender. When enrollment had reached 23 children, FDA was consulted via teleconference (February 8, 2001) to review the status of this study. It was agreed that the study could be halted at the current enrollment of 23 as an adequate number of children aged 2 and 3 years (n=10) had been enrolled.

Study AQ-00-04 compared the ibuprofen/pseudoephedrine suspension to pseudoephedrine alone in children aged 2-5 years with symptoms of an acute upper respiratory infection. The pharmacokinetic properties of pseudoephedrine when administered in the combination suspension were similar to those when administered alone, in symptomatic children aged 2-5 years. Comparison of the pharmacokinetic parameters measured in study AQ-99-02 (healthy children 6-11 years old) with those in study AQ-00-04 (symptomatic children 2-5 years old) demonstrated that the rate and extent of absorption of both ibuprofen and pseudoephedrine in the 2-5 year old age group were within ±35% of the respective parameters for the 6-12 year old age group as discussed with the Agency. Therefore the bioavailability is similar across the age range of 2-12 years old.

Adverse events

All subjects in the study had upper respiratory infections as required by protocol. At baseline the most common symptoms were runny nose (83%), followed by sneezing (65%), wet cough (52%), and nasal congestion (48%). There were no statistically significant differences between the two groups except for head fullness and earache, where marginal differences were observed, and wet cough, where significant differences were observed. For all 23 subjects who received study medications, adverse experiences reported during the study are listed by body system in Table 1. There were no significant differences between the two treatment groups for any adverse experiences.

Three (27.3%) subjects reported three adverse events (one instance each of chills, rhinitis, and otitis media) in the ibuprofen/pseudoephedrine hydrochloride group, while six (50%) subjects reported seven adverse experiences (one instance each of asthenia, pain, abdominal pain, increased appetite, and rash, and two instances of hypertension) in the pseudoephedrine hydrochloride alone group. Eight of the adverse experiences were rated as mild in severity and the remaining two (otitis media reported by a subject receiving ibuprofen/pseudoephedrine hydrochloride and abdominal pain reported by a subject receiving pseudoephedrine hydrochloride alone) were rated as moderate. Except for rhinitis and asthenia, all the adverse experiences were considered not to be related to study medication. The incidence of rhinitis,

reported by a subject receiving ibuprofen/pseudoephedrine hydrochloride, was considered possibly related to study medication. The incident of asthenia, reported by a subject receiving pseudoephedrine hydrochloride alone, was considered remotely related to the study medication. There were no serious adverse experiences or deaths. None of the subjects discontinued due to an adverse experience.

MO Comment: The types and frequencies of AE incidences reported in the pharmacokinetic studies are supportive of safety of the combination drug.

Table 1 Summary by Severity, AQ-00-04. A subject may have multiple AEs.

Adverse Experiences(AEs) (by Body System and COSTART Term)	Advil C&S Suspension (n=11) N (%)	SEVERITY Mild	Mod	Sev	Unk	Sudafed (n=12) N (%)	SEVERITY Mild	Mod	Sev	Unk	p-value +
ANY BODY SYSTEM											
No. of AEs**	3	2	1	0	0	7	6	1	0	0	
No. of Subjects**	3 (27.3)					6 (50.0)					0.400
Body as a Whole											
ASTHENIA	0 (0.0)	0	0	0	0	1 (8.3)	1	0	0	0	1.000
CHILLS	1 (9.1)	1	0	0	0	0 (0.0)	0	0	0	0	0.478
PAIN	0 (0.0)	0	0	0	0	1 (8.3)	1	0	0	0	1.000
No. of AEs**	1	1	0	0	0	2	2	0	0	0	
No. of Subjects**	1 (9.1)					2 (16.7)					1.000
Cardiovascular											
HYPERTENSION	0 (0.0)	0	0	0	0	2 (16.7)	2	0	0	0	0.478
No. of AEs**	0	0	0	0	0	2	2	0	0	0	
No. of Subjects**	0 (0.0)					2 (16.7)					0.478
Digestive											
ABDOMINAL PAIN	0 (0.0)	0	0	0	0	1 (8.3)	0	1	0	0	1.000
INCREASED APPETITE	0 (0.0)	0	0	0	0	1 (8.3)	1	0	0	0	1.000
No. of AEs**	0	0	0	0	0	2	1	1	0	0	
No. of Subjects**	0 (0.0)					2 (16.7)					0.478
Respiratory											
RHINITIS	1 (9.1)	1	0	0	0	0 (0.0)	0	0	0	0	0.478
No. of AEs**	1	1	0	0	0	0	0	0	0	0	
No. of Subjects**	1 (9.1)					0 (0.0)					0.478
Skin and Appendages											
RASH	0 (0.0)	0	0	0	0	1 (8.3)	1	0	0	0	1.000
No. of AEs**	0	0	0	0	0	1	1	0	0	0	
No. of Subjects**	0 (0.0)					1 (8.3)					1.000
Special Senses											
OTITIS MEDIA	1 (9.1)	0	1	0	0	0 (0.0)	0	0	0	0	0.478
No. of AEs**	1	0	1	0	0	0	0	0	0	0	
No. of Subjects**	1 (9.1)					0 (0.0)					0.478

IV. Clinical Data and Sources

The following three clinical studies were performed for the present application:

AQ-99-02: A Single-Dose, Randomized, Open-Label, Single Center, Three-Way Crossover Pharmacokinetic Study of Children's Advil ® Cold in 6 to <12 year Old Children (medication was given to 29 healthy children).

AQ-00-04: A Single-Dose, Randomized, Open-Label, Multicenter, Parallel Group Confirmatory Pharmacokinetic Study of Children's Advil Cold in 2 to <6 Year Old Children (medication was given to 23 children with symptoms of acute respiratory infection).

AQ-99-03: Children's Advil Cold Multiple-Dose Safety Study in Children 2 to <12 Years Old (106 subjects enrolled).

The integrated review of safety (§VII) also includes a worldwide safety surveillance overview from the Sponsor and from SRS/AERS.

V. Clinical Review Methods

The clinical trials, SRS and AERS data, literature, and reports from DAWN and AAPCC were reviewed for this application.. There was no DSI audit for the safety study AQ-99-03. The sponsor submitted financial disclosure and debarment statements.

VI. Integrated Review of Efficacy

This application did not include any efficacy trials. The efficacy of pseudoephedrine was recognized by inclusion in the Final Nasal Decongestant Monograph in 1994. The Sponsor referred to NDAs 18-989, 19-771, 20-589, 20-267, 20-812, and 20-944 to support safety and efficacy of ibuprofen and the ibuprofen/pseudoephedrine hydrochloride combination product.

VII. Integrated Review of Safety

This section will review the safety study AQ-99-03 and then present results of worldwide post-marketing surveillance. For the three clinical trials included in this application, there were a total of 156 children who used the combination drug for up to seven days, with a favorable adverse event profile.

A. Safety Study AQ-99-03

This was an open-label, multiple-dose, single treatment, multicenter study of Children's Advil ® Cold in children 2 to <12 years old. The study was performed at two sites during the period July 17, 2000—December 19, 2000. The investigators were Claude B. Prestidge, MD at site 1, Radiant Research, Inc., Dallas, TX, and Samantha Bostrom, MD at site 2, Radiant Research, Inc., Salt Lake City, UT.

Objective

The objective of the study was to characterize the adverse experience profile of Children's Advil Cold (ibuprofen — _ pseudoephedrine hydrochloride 15 mg/5 mL) and to demonstrate its safety in the 2 to <12 year-old target population. Efficacy was not evaluated in this study.

Method

This was an open-label, uncontrolled safety study. The study enrolled 106 subjects aged 2 to <12 years of age. The study medication was Children's Advil Cold (ibuprofen — mg/pseudoephedrine hydrochloride 15 mg/5 mL;) administered orally via a dosing cup. Dosing

was directed at every 6 hours, as needed, up to four times a day, for no more than 7 days for symptoms of a cold, or for no more than 3 days for a fever. Vital signs (systolic and diastolic blood pressure, pulse rate, respiration rate, and oral temperature) were obtained at baseline, at Visit 2 (after the second day's dosing), and at Visit 3 (at the end of study participation). In addition, adverse experiences were recorded by the parent/guardian in a daily diary.

The parent/guardian was presented with and reviewed a copy of the product's proposed labeling to determine whether or not their child was qualified to participate based on the product's labeling. Following informed consent/assent, a medical history including questions regarding the use of analgesic and decongestant products during the prior three months and menarche history, if applicable, was obtained. Entrance eligibility of potential subjects was determined by the Investigator following a physical examination including a pregnancy test, if appropriate (laboratory tests were not required).

The parent/guardian of eligible subjects was given two bottles with 4 oz of study medication (for subjects weighting 24-47 pounds) or three bottles with 4 oz (for subjects weighting 48-95 pounds), a copy of the product's proposed labeling, and a diary. Prior to discharging the parent/guardian/subject from the study site, the investigator/designee reviewed with the parent/guardian the dosing instructions, the return visit schedule, and the directions for completing the daily diary.

The dose of study medication was 1 teaspoon for subjects weighing 24-47 pounds and 2 teaspoons for subjects weighing 48-95 pounds. The subject was to receive the same dose every six hours, as needed, up to four times a day, for no more than seven days for symptoms of a cold, or for no more than three days for a fever. The parent/guardian was instructed to return with the subject to the study site following the second day's dosing for monitoring of the subject's vital signs.

For each day the study medication was administered, the parent/guardian was to record the amount and time of each dose and respond to the question "has your child experienced anything different while taking the medicine?" If "anything different" had occurred, the parent/guardian was to provide information about what happened, the frequency of the occurrence, when it happened, how long the experience lasted, "how bad" the experience was, what, if anything, was done for the experience, had the experience occurred with other medications, and what, if any, concomitant medications the subject was taking.

The parent/guardian was instructed to return all bottles of study medication (both used and unused) and the daily diary at the completion of the study (i.e., after the 7- day dosing period or any time study participation was discontinued). Upon return to the study site, the investigator or appropriate designee reviewed with the parent/guardian all information contained in the daily diary and recorded all adverse experience data on the appropriate page of the case report form. The investigator reviewed the start and stop dates and times, and determined the drug relatedness, action taken, and whether present pre-study for each adverse experience.

MO Comment: Although the Sponsor referred to this study as an actual use study, it was not. Subjects were coached by study professionals as to proper dosing and use. This coaching is not representative of actual use and would be expected to improve results by improving understanding of and compliance with directions.

Subjects were eligible for **inclusion** in the study provided they met all of the following criteria:

- for males or females, age 2 to <12 year;
- presence of symptoms associated with the common cold, sinusitis or flu including headache, fever, nasal congestion, body aches and pains with an onset within four days before the first dose of the study medication;
- in general good health as judged by the investigator after completing the physical examination;
- the parent/guardian read the product's proposed labeling and agreed the subject's participation is appropriate under the product's labeling;
- parent/guardian was able to read, comprehend, and sign the informed consent form and children provided their assent, if appropriate.

Subjects were **excluded** from participating in the study if any of the following were noted:

- weight <24 pounds or >95 pounds;
- hypersensitivity to aspirin, pseudoephedrine hydrochloride, ibuprofen, or any other nonsteroidal anti-inflammatory agent;
- history of melena or any significant hepatic, renal, endocrine (e.g., diabetes, thyroid disorder), cardiac (e.g., hypertension), neurological (e.g., epilepsy), psychiatric, gastrointestinal, pulmonary (e.g., asthma, chronic bronchitis), hematologic or metabolic disorders;
- any serious medical condition or history felt by the Investigator to place the subject at increased risk;
- concurrent use of any other cough/cold medication (i.e., antihistamine, analgesic, decongestant) within 12 hours prior to the first dose of study medication (concomitant use of antibiotics will be permitted);
- use of a monoamine oxidase inhibitor and/or sympathomimetics or other stimulating drugs for the treatment of attention deficit hyperactivity disorder within two weeks of the first dose of study drug administration;
- female who has experienced menarche and has a positive pregnancy test at the time of screening;
- have taken an investigational drug within the past 30 days;
- have already participated in this trial;
- are relatives of the investigator or Sponsor, or any personnel of study site who are directly involved in the study.

Data on dosing and adverse experiences were recorded in a daily diary given to the parent/guardian at enrollment. For each day of the study, whether or not study medication was

given, the parent/guardian was asked if the child needed study medication, if yes, why was the child dosed (i.e., for a cold, fever, or both), and to record the time and amount of each dose for the day. The parent/guardian was also specifically asked whether "your child experienced anything different while taking the study medication?" and whether the "child took any other medication (other than study medication) today?". If the child had experienced "something different, " the parent/guardian was asked what the medical problem or symptom was and further details: when the condition started, did it stop, what was the severity, whether the condition needed to be treated, and if this experience had happened while taking any other medication. The parent/guardian was instructed in the diary to use the following descriptions of "mild," moderate," and "severe" to classify the severity of the adverse experience:

mild - the child is aware of the symptom but it is easily tolerated;

moderate – the child feels enough discomfort to interfere with usual activities;

severe – the child is unable to do usual activities.

The parent/guardian was instructed to record in the diary all adverse experiences during the 7-day study period. Details about any recorded adverse experience were obtained from the parent/guardian at the return visit interview. The investigator reviewed the start and stop dates and times, action taken, whether present pre-study, and determined the drug relatedness for each adverse experience.

The use of concomitant and/or rescue medications was neither encouraged nor prohibited. Any medications given during the seven-day study, including those given for unrelieved symptoms, were to be recorded in the subject diary.

An *evaluable subject* was defined as any subject who completed the baseline physical examination and took at least one dose of study medication over the maximum seven-day dosing period. A *completed subject* was defined as any subject who completed the baseline physical examination, took a minimum of four doses of study medication over the first two days of dosing, returned to the clinic for monitoring of vital signs at Visit 2, returned to the clinic at the end of the study (Visit 3), and completed a physical examination and monitoring of vital signs.

Results

A total of 106 subjects enrolled at two sites (see Table 2). The vast majority of subjects enrolled at site 2. As a result of a change in the site coordinator, enrollment at Site 1 was discontinued after six subjects because of poor record keeping and lack of cooperation by study site personnel. Six subjects were discontinued from the study: three due to protocol violations (subjects no. 10001, 10004, 10005 all took a cold/cough medication within 12 hours prior to taking study medication); two subjects were lost to follow-up (subjects no. 20035 and 20117); one subject discontinued due to an adverse experience (subject no. 20149).

An approximately equal number of males (47.1%) and females (52.9%) participated in the study. The mean age of the subjects was 5.7 years. The majority of subjects were Caucasian (74.0%), followed by "other" (12.5%), Hispanic (10.6%), and Black (2.9%). Subject weights and heights were: 47.8 pounds mean (range: 24-86 pounds) and 45.3 inches mean (range: 33-60 inches), respectively. 51 subjects (49%) were less than six years-old, and 53 subjects (51%) were aged six to <12 years. Twenty-eight subjects (27%) were two-to-three years of age.

Table 2. Subject disposition, AQ-99-03

Status	Site 1	Site 2	Total
Enrolled	6	100	106
Completed	2	76	78
Evaluable	6	98	104
Discontinued	3	3	6

Protocol violations involved inclusion/exclusion criteria, deviations in the timing of Visits 2 and/or 3, dosing deviations, and drug accountability deviations. The Sponsor did not consider these protocol violations to affect the outcome of the study:

- Subject 10002 entered the study with an onset of symptoms five days prior to the first dose of study medication; the inclusion criterion specified onset of symptoms within four days of the first dose of study medication.
- Subject 20136 took Ritalin four days prior to entering the study. An exclusion specified that MAOI drugs and/or sympathomimetics or other stimulating drugs for the treatment of attention deficit hyperactivity disorder were not to be used within two weeks of the study. This subject did not report any AE (FDA comment).
- Subject 20112 was the child of one of the subinvestigators at Study Site 2.
- Visit 2 was scheduled following the second day's dosing for monitoring of vital signs. Subject 10002 did not return to the clinic for Visit 2; subjects 20017 and 20122 had Visit 2 combined with Visit 3; subject 20146 returned for Visit 2 the day after the last dose of study medication was taken on day 7. Visit 3 was scheduled within two to three days after their last dose of study medication, but 17 subjects returned for Visit 3 more than three days after their last dose of study medication.
- Three subjects were administered an incorrect dose. Subjects weighing between 24 and 47 pounds were to receive one teaspoon of study medication per dose. Subjects 10004 and 10005 were dosed with 1.5 teaspoons and subject 20046 was dosed with 0.5 teaspoons for one dose (study day 1, dose three).
- Study medication was to be administered every six hours, as needed. Out of a total of 925 doses of study medication administered, 67 (7.2%) were administered prior to the six-hour dosing interval.
- After Visit 3, the quantity of medication returned was measured using a graduated cylinder. A greater than 10% difference between the amount of medication actually returned and the amount expected based on the number and amount of medication administered was interpreted as a deviation from the protocol. Eighteen subjects returned less medication than expected, ranging from 13.5% to 32%.

MO Comments: Protocol violations were generally minor. The very small number of subjects enrolled at Site 1 made the study effectively a single center study. Dosing compliance was excellent, possibly due to familiarity with the medication and instruction by the staff. Only two of the subjects who returned less medication than expected also reported AEs, one somnolence and one backache.

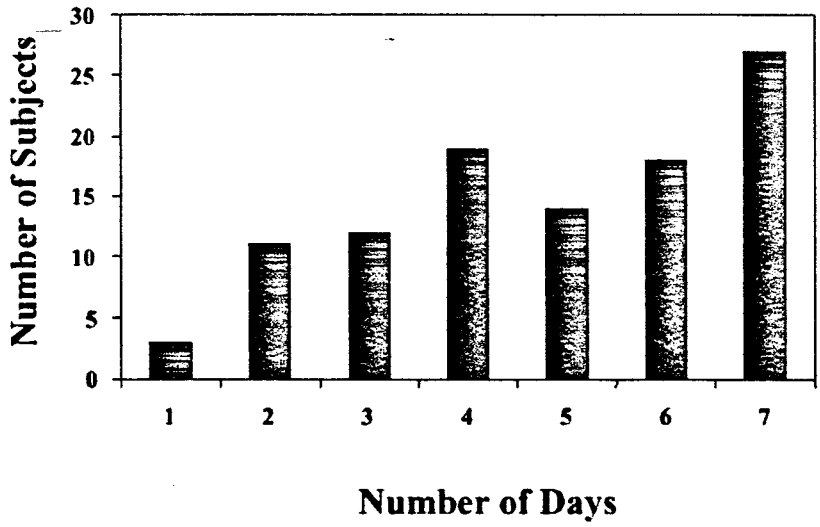

Figure 1. Number of days study drug was taken, AQ-99-03

Other than the condition being treated for the study, 60 of the 106 entered subjects (57%) had past medical conditions and 69 (65%) had current medical conditions. Past/current medical conditions of note included asthma/reactive airway disease (n=17), otitis media (n=23), strep throat (n=5), and sinusitis (n=2). Concomitant medication use included antibiotics (n=22), corticosteroids (n=4), beta agonist (n=3), antihistamine (n=1), leukotriene receptor antagonist (n=1), and a mast cell stabilizer (n=1).

The presence of symptoms of cold, flu, or sinusitis was an inclusion criterion for the study. The most frequently occurring symptoms at baseline were nasal congestion (85%), runny nose (66%), dry cough (42%), sore throat (37%), and earache (12%). Seven subjects (7%, FDA analysis) had a fever (oral temperature >100°F) at baseline.

Study drug was administered an average of 4.8 days (Figure 1), and subjects were administered an average of 8.9 doses (Figure 2).

MO Comment: No analysis was performed to check if subjects took the medication for longer than 3 days for a fever. Only 7subjects had temperatures over 100°F at entry into the trial. A total of 27 subjects took the drug for 7 days, and the study design did not address the possibility that consumers might use the product for longer than the recommended duration. Due to the limited exposure of subjects with fever and subjects who used the drug for 7 days, there is insufficient data to support a 7 day duration of use for children. (The data for Figure 1 and Figure 2 do not look the same. Why is that? The data should be the same for days 1-7.)

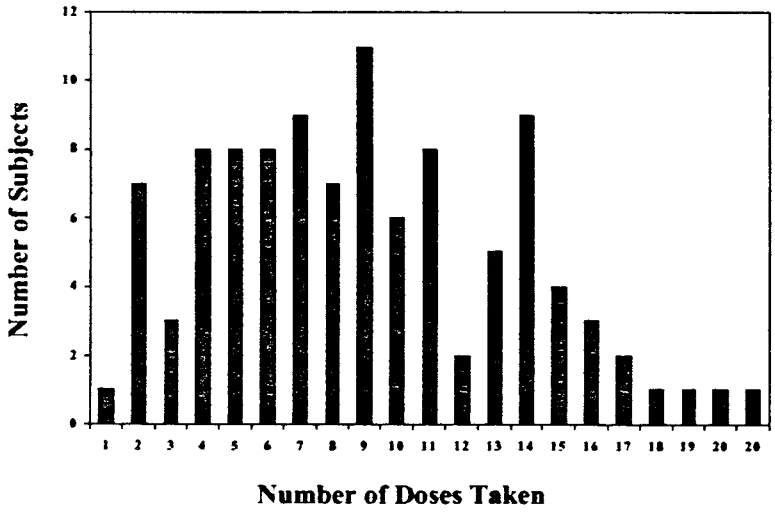

Figure 2. Number of doses taken, AQ-99-03

Table 3 shows that a total of 38 adverse experiences were reported by 29 of the 104 evaluable subjects (28%). Adverse experiences were most frequently associated with the nervous system (n=11). The most frequently reported adverse experience was somnolence (n=7)

Table 3. Number of AEs by body system, AQ-99-03

BODY SYSTEM	Number of Adverse Experiences Reported	Number of Subjects Reporting Adverse Experiences
Body as a Whole	8	8
Digestive	9	6
Hemic/Lymphatic	2	2
Nervous	11	10
Respiratory	1	1
Skin/Appendages	2	1
Special Senses	5	5
ANY BODY SYSTEM	38	29

followed by vomiting (n=3). Each of the following symptoms had an incidence of two: asthenia, fever, abdominal pain, nausea, tremor, and otitis media. The remaining adverse experiences were single occurrences: back pain, common cold, headache, pain, diarrhea, dyspepsia, lymphadenopathy, lymphocytosis, hyperkinesia, nervousness, rhinitis, pruritus, rash, conjunctivitis, ear disorder, and ear pain.

Of the 38 occurrences of adverse experiences, 20 were rated as "mild," 16 were rated as "moderate," and two were rated as "severe." The "severe" adverse experiences were single occurrences of somnolence and ear pain. Twelve of the 38 adverse experience occurrences were considered by the investigator to have a relationship to the study medication: somnolence (n=3), tremor (n=2), and single occurrences of asthenia, headache, vomiting, nausea, abdominal pain, hyperkinesia, and nervousness.

The vital sign data for the 78 completed subjects were recorded at Visit 2 following at least four doses of study medication. Other than an antipyretic effect at Visit 2, oral temperature returned to normal in five of six subjects with fever at baseline, and there were no clinically significant changes in vital signs for either completed or evaluable subjects (see Table 4).

There were no serious adverse experiences reported during this study. One subject was

	Completed Subjects (n=78)			Evaluable Subjects (n=104)		
Vital Sign	BL	Visit 2	Visit 3	BL	V. 2	V. 3
Systolic BP (mmHg)	97±9	93±8	94±7	96±9	93±9	94±7
Diastolic BP (mmHg)	62±8	59±8	61±6	61±7	58±6	60±6
Heart Rate (bpm)	87±10	86±9	84±9	88±12	86±10	85±10
Respiration Rate (bpm)	22±4	23±3	22±3	22±4	23±3	22±3
Oral Temp. (°F)	98.2±1.1	97.8±0.7	97.8±0.8	98.2±1.1	97.8±0.8	97.9±0.9

Table 4. Vital signs for completed and evaluable patients, at baseline , visit 2 and visit 3, AQ-99-03

discontinued from the study due to an adverse experience. Subject 20149 was reported by the

parent/guardian to have felt "shaky" 2 hours after taking the first dose of study medication and again on the second day of the study 1 hour 40 minutes following dosing. The parent discontinued study medication, and the subject's shakiness resolved spontaneously. This was rated by the study physician as probably related to study medication.

Summary of Results

A total of 28% of evaluable subjects reported adverse experiences. The majority of these (53%) were mild in nature and not thought by the investigator to be related to the study medication (68% of the adverse experiences were rated as unrelated to study medication). There were no serious adverse experiences, no hospitalizations, and no treatments were required for any adverse experience. No clinically significant changes in vital signs were noted in "all" subjects as well as the group of "completing" subjects that was administered a minimum of four doses of study medication in the first two days of the study.

With the exception of three subjects, the parents followed the label directions correctly and administered the weight/age appropriate dose to the child. No child received more than four doses of study medication per day, and 93% of the doses were administered 6 hours or more following the previous dose. No parent administered more than four doses in any one 24-hour period.

The three subjects (3%) mentioned above were administered an incorrect dose: two, a half teaspoon more than recommended (one received 14 doses over seven days and one received 10 doses over seven days) and one, a half teaspoon less than recommended for one dose only. The two subjects who received a half teaspoon more than recommended reported no adverse experiences. These results indicate that the consumers used the product appropriately. However, subjects in this study received coaching on proper use of the medication.

The Sponsor concluded that the results of this study demonstrate that a suspension formulation of ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg/5 mL is safe for use in children aged two to <12 years for the treatment of symptoms of the common cold, sinusitis or flu including headache, fever, nasal congestion, body aches and pains. Adverse experiences reported were generally mild and unrelated to study medication. Additionally, ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg/5 mL combination suspension had no clinically significant effect on vital signs (i.e., blood pressure, pulse rate, or respiration rate).

MO Comment: The reported 28% incidence of AEs is typical of clinical trials with similar methods for eliciting adverse experiences. Several of the reported AEs may be due to the presenting condition. The results of this study are supportive of safety, however the study was limited to 7 days of follow-up.

B. Safety in Overdose

Data from the American Association of Poison Control Centers (AAPCC) were reviewed for 1994 through 2000. Outcomes for the combination of ibuprofen and pseudoephedrine hydrochloride, the concomitant ingestion of ibuprofen and pseudoephedrine hydrochloride, and the individual ingredients were examined, with and without ingestion of other concomitant drugs. Prescription and nonprescription doses were included.

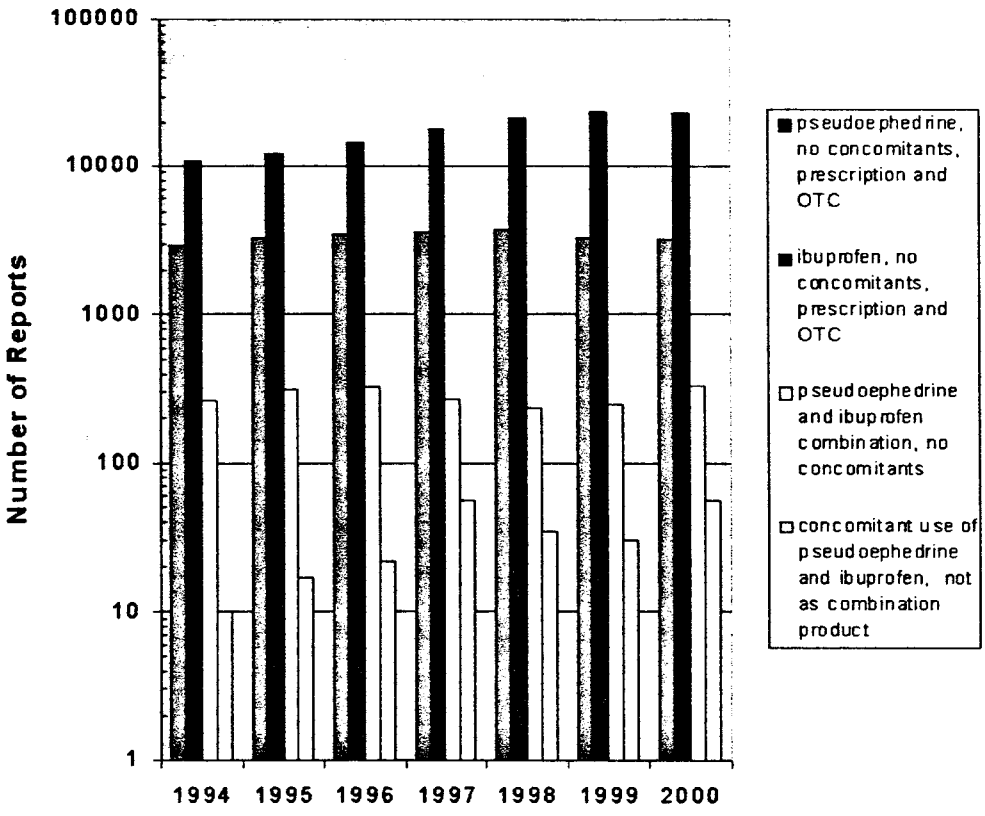

Figure 3. American Association of Poison Control Centers, reports for patients 2 to <12 years of age; prescription and OTC products, intentional and unintentional exposures included.

Figure 3 shows the number of poisoning exposures (contacts) to the AAPCC for 1994-2000 for subjects whose age is 2 to <12 years. On a year-to-year basis, more than 99% of the exposures in Figure 3 were classified as "unintentional ingestion", including unintended misuse, therapeutic error. Intentional ingestion was defined to include intentional misuse, abuse, and suicide attempt.

As shown in Figure 3, the number of poison exposures for ibuprofen-containing single ingredient products has increased steadily from 10,929 exposures in 1994 to 23,524 exposures in 1999. However, the number of reports for pseudoephedrine single ingredient products has remained relatively constant (about 3000), as has the number of reports for ibuprofen with pseudoephedrine combination products (about 300).

MO Comment: The high preponderance of unintentional ingestion among poison reports for ibuprofen and/or pseudoephedrine in 2 to <12 year olds indicates a low abuse potential, but the increase in reports for single ingredient ibuprofen-containing products may reflect increased use or availability of ibuprofen-containing products OTC since 1995. This warrants further postmarketing surveillance.

No fatalities were reported for the combination of ibuprofen and pseudoephedrine hydrochloride or their concomitant ingestion. One fatality was reported in 1997 for single ingredient ibuprofen ingestion. The number of major outcomes for 1994-1999, defined as signs or symptoms as a

result of the exposure that were life-threatening or that resulted in significant residual disability, was a total of 4 for pseudoephedrine and 7 for ibuprofen single ingredient products (2 and 5 respectively, for reports without use of concomitant medications). There were no major outcomes for the combination products.

The 11 major outcomes are presented as line listings in Table 5. In 10 of 11 cases, the reporter considered the clinical effects to be related to the drug. For the combination of ibuprofen and pseudoephedrine, there were no major or death outcomes in any of the years reviewed. One death occurred in a 2 year old in 1997 who received ibuprofen and died from anaphylactic shock. This subject had a history of facial swelling after receiving ibuprofen one month earlier.

Table 5 Major Outcomes reported by AAPCC 1994-1999, for children 2 to <12 years of age

Serial #	Date	Age	Gender	Reason	Clinical Effects	Relatedness	Concomitant Drugs
IBU alone							
031-18300736	6/9/94	6	M	Unknown	Coma, Drowsiness, Lethargy	Related	
110-4005436	4/22/95	3	M	Accidental	Unknown	Unknown	
008-889333	4/4/96	9	M	Accidental	Dermal Irritation/pain, rash, ocular pain, pupils non-reactive	Related	
012-4107283	1/23/96	7	F	Adverse Reaction	Seizures (multiple/discrete)	Related	
102-9109741	10/4/97	11	F	Intentional - suspected suicide	Other LFT abnormality; Other miscellaneous effect	Related	
IBU with concomitant							
040-2144665	4/1/95	3	F	Accidental	Ataxia, Coma, Drowsiness/lethargy, slurred speech	Related	Ibuprofen Rx, other dextromethorphan - containing preparation
003-23106594	7/4/95	7	M	Adverse Reaction	Increased Bilirubin, Other LFT abnormality	Related	Acetaminophen: adult formulation, ibuprofen Rx
PSE Alone							
014-229101	5/13/97	3	F	Accidental	Dehydration, vomiting, drowsiness/lethargy	Related	
072-4205848	10/14/98	7	F	Accidental	Tachycardia, erythema/flushed, hallucinations/delusions	Related	
PSE With concomitant							
081-2319187	4/25/97	11	F	Intentional - suspected suicide	Hypertension, Tachycardia	Related	Corticosterioids
011-2676054	1/4/98	2	M	Accidental	Drowsiness/lethargy	Related	Unknown type of APAP only formulation

Poisoning reports from AAPCC for subjects aged 12 years or more were also reviewed. From 1994-1999, the numbers of reports for simultaneous use of ibuprofen and pseudoephedrine products totaled 247. In this period, the poisoning reports for ibuprofen-pseudoephedrine combination products, without concomitant medications, totaled 609. There were no deaths and one major outcome for the combination product or for concomitant use of both ingredients.

The proportion of intentional exposures in the >12 years age group was much higher than in the younger age group. The fraction of unintentional exposures for combination products without concomitant medication varied from 41.02% (in 1995) to 54.7% (in 1997) for subjects 12 years old or more, while it was >99% in subjects from 2 to < 12 years old.

MO Comment: Comparison of the AAPCC data for the two age groups shows that there are differences in overdose and abuse patterns. The number of poisoning reports for use of combination drug products was more than twice as great (1653 versus 609) in the younger group (2 to less than 12) than in older subjects, whereas the number of reports for concomitant use was much fewer (168 versus 247). Intentional exposures were very uncommon (<1%) in the younger age group but much more common (up to half or more) for older subjects. The usage

differences may be explained by the following: doses in the younger age group are mostly administered by caregivers or parents, and an adult formulation may have been administered since no pediatric combination product was available prior to 2000. In addition, some older subjects may ingest the product with suicidal intent. Overdoses in the 2 to <12 year age group are mainly unintentional and probably result most often from accidents and or care-giver errors. This situation may improve with OTC availability of pediatric combination products, but if not, then improved labeling may be needed in the future to reduce such overdoses.

Figure 4 shows the number of poison exposures recorded by the AAPCC for subjects < 2 years old. On a year-to-year basis, more than 99% of the exposures in Figure 4 were classified as "unintentional ingestion".

Also seen in the < 2 year old group as well as in the 2 to < 12 year old group were increases in the poisoning reports for the single ingredient products. From Figure 4, the number of reports in < 2 year olds for ibuprofen single ingredient products more than doubled from 1994 to1999, increasing every year. The number of reports for pseudoephedrine single ingredient products increased approximately 30% (from 1,155 exposures in 1994 to 1,508 exposures in 1999). Nearly all the exposures (>99%) were classified as unintentional. There was 1 death in 1997 and another death in 1994, both involving ibuprofen exposure with concomitant medications. Major events totaled 3 for pseudoephedrine and 11 for ibuprofen (1 and 9, respectively, for exposures without concomitant medications).

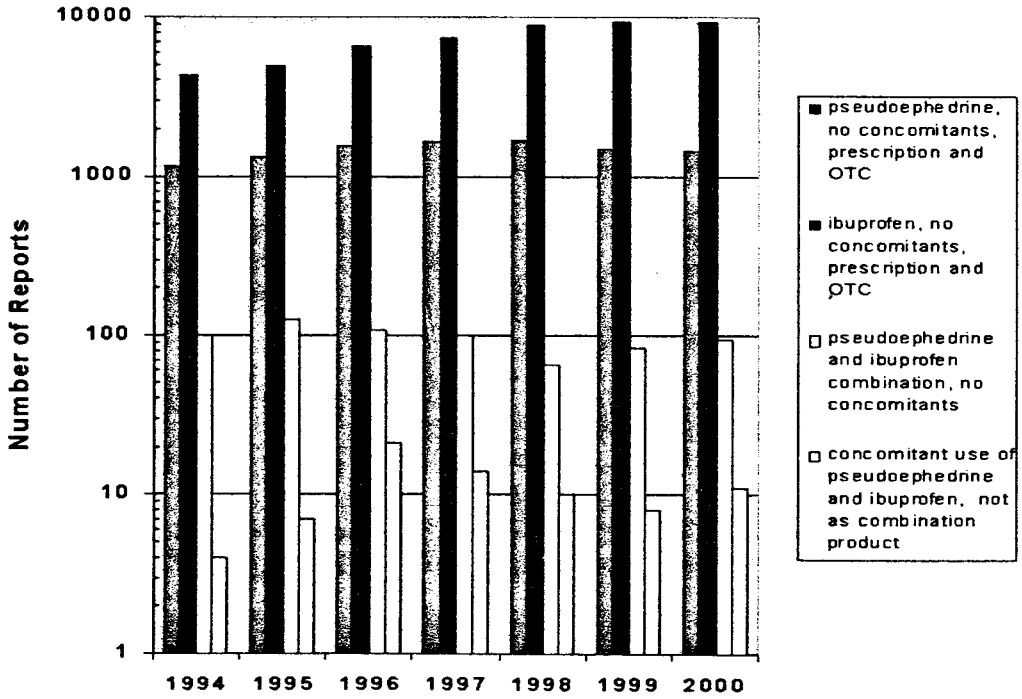

Figure 4. AAPCC poisoning reports in subjects < 2 years old (compare Figure 3).

MO Comment The overdose patterns for <2 year olds are very similar to those for the targeted population of 2 to <12 year olds. For each year from 1994 to 1999, the number of reports in <2 year olds was within the range 39% to 46% of the number of reports in 2 to <12 year olds, for either single ingredient products containing ibuprofen or pseudoephedrine. The ratios of the number of reports for the combination in the two age groups behaved similarly, but with more statistical variability that was associated with the smaller numbers of reports

During the past six years, there were no fatal outcomes reported for exposures associated with the drug combinations. Overall, three fatalities were reported by AAPCC in children less than 12 years old; all involved single ingredient ibuprofen. Two were subjects less than 2 years old, occurring in 1994 and in 1997. No further information on this 1997 death was provided. The third fatality in 1997 was a subject in the 2 to less than 12-year age range. This 2-year-old boy with gastroenteritis was treated with ibuprofen suspension. He had a history of facial swelling approximately 1 month earlier after receiving a dose of ibuprofen. On the first day of ibuprofen treatment for the incident illness, he received two doses, 1 teaspoon and then ¾ teaspoon. He received an additional ¾ teaspoon the second day. Facial swelling developed. He was seen by his physician and ibuprofen was discontinued. That evening he was moaning and drawing up his legs as if in pain. Acetaminophen was given. On the evening of the third day he was pale with wheezing and gasping respirations. Apnea ensued. CPR was initiated by his father and full resuscitation attempted in the Emergency Department, without success. The postmortem examination attributed the death to anaphylactic shock.

The 1994 fatality was a 12-month-old girl who was brought to the Emergency Department about 12 hours after ingesting an unknown quantity of ferrous sulfate tablets. She was transferred to a tertiary care hospital where 32 of 45 ferrous sulfate tablets were removed from her stomach. Whole bowel irrigation, a bicarbonate infusion and deferoxamine were initiated. Abdominal distention was noted about 12 hours after admission. Serum iron at that time was 561 micrograms/dL. An ibuprofen level was noted to be 105 microgram/mL although no history of ingestion or use was evident. Despite continuing efforts, including surgical relief of the bowel obstruction, the child died approximately 66 hours after the ferrous sulfate tablet ingestion.

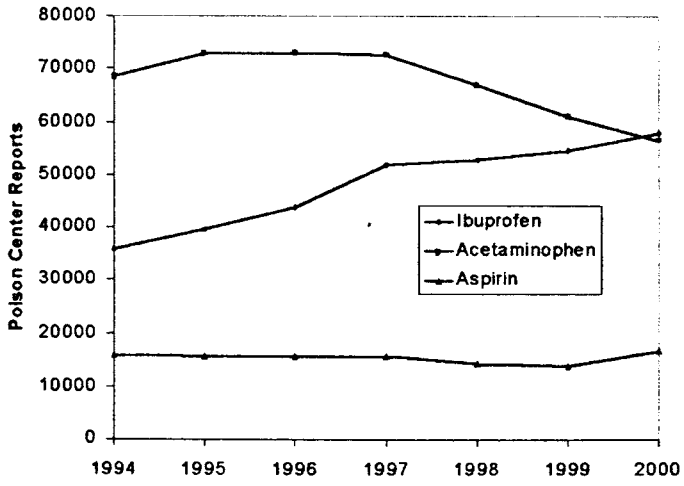

Figure 5. AAPCC reports for single ingredient products, all age groups

Figure 5 plots trends in the numbers of poisoning reports in all age groups for aspirin, acetaminophen and ibuprofen using data from Table 6 supplemented by year 2000 data from AAPCC. The number of reports for ibuprofen increased from 1994 to 2000, while at the same time the number for aspirin changed relatively little and those for acetaminophen decreased. The numbers of reports for acetaminophen peaked during 1995 through 1997 while those for aspirin remained almost constant.

When examined in the context of exposure and outcome data for acetaminophen and aspirin, the relative safety of ibuprofen is evident. Table 6 presents data for all age groups, comparing poison reports for ibuprofen, acetaminophen and aspirin. In each of the years 1994-1999, deaths for acetaminophen and aspirin far outweigh those for ibuprofen.

Table 6 also shows differences in overdose patterns for ibuprofen, acetaminophen and aspirin. Data from Table 6 were combined for years 1994-2000 to obtain the results in Table 7. The

Table 6. AAPCC poison reports, 1994 – 1999, single ingredient preparations in all age groups.

			Ingestion Category		Outcome Classification	
Year	**Substance**	**No. of Exposures**	**Unintentional†**	**Intentional***	**Major~**	**Death**
1999	Ibuprofen	54,643	41,986	11,678	105	3
	Acetaminophen	61,092	43,293	17,122	740	85
	Aspirin	13,854	6,236	7,226	251	45
1998	Ibuprofen	52,751	39,397	12,425	97	4
	Acetaminophen	66,885	47,544	18,671	723	70
	Aspirin	14,263	6,062	7,822	222	33
1997	Ibuprofen	51,738	37,434	13,203	95	6
	Acetaminophen	72,580	51,665	20,063	566	65
	Aspirin	15,648	7,072	8,158	162	44
1996	Ibuprofen	43,777	29,453	13,378	88	3
	Acetaminophen	72,947	51,037	21,065	533	53
	Aspirin	15,516	6,373	8,675	146	46
1995	Ibuprofen	39,361	24,815	13,639	80	6
	Acetaminophen	72,889	51,450	20,730	501	55
	Aspirin	15,548	6,220	8,924	164	48
1994	Ibuprofen	35,703	22,285	12,723	76	3
	Acetaminophen	68,496	48,604	19,281	483	59
	Aspirin	15,890	6,264	9,237	143	40

†Unintentional ingestion as defined by the authors includes: general, therapeutic error, unintentional misuse, environmental, bite/sting, misuse, food poisoning, occupational, unknown.

*Intentional ingestion as defined by the authors includes: intentional misuse, abuse, and suicide attempt, unknown.

~Major outcome as defined by the authors includes: signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability.

fraction of unintentional exposures is almost the same for ibuprofen and acetaminophen at about 70%, while the fraction is much lower for aspirin (~42%). The incidences of major outcomes at 0.23% and deaths at 0.009% are much lower for ibuprofen than for acetaminophen and aspirin.

Table 7. Exposure and Outcome Summary from AAPCC Reports

1994-2000	Unintentional Exposures, % of Total	Major Outcomes, % of Total Exposures	Deaths, % of total exposures
Ibuprofen	70.4	0.23	0.009
Acetaminophen	70.0	0.93	0.10
Aspirin	42.1	1.29	0.29

MO Comment: The AAPCC data support the relative safety of ibuprofen in comparison to aspirin and acetaminophen. The several times lower rates of major outcomes and deaths, on a per exposure basis, for ibuprofen indicates a greater therapeutic margin in overdose. The lesser differences in incidence of major outcomes and death between aspirin and acetaminophen may be partially accounted for by the difference in rates of unintentional exposure: aspirin is used more by adults. If ibuprofen is compared with acetaminophen, for which the rate of unintentional exposures is similar, ibuprofen is associated with a much lower incidence of major outcomes and deaths, supporting its safety. It is cautioned, however, that the data in Table 6 included primarily adult uses. Pediatric overdose patterns are different, especially in children <12 years of age. Also, the overdose patterns changed during the period 1994-2000, with an increase in ibuprofen poisonings relative to those for acetaminophen and aspirin. Of note, pediatric ibuprofen was first approved OTC in 1995, and the increase in reports in 1996 may reflect an increase in usage.

C. Abuse Potential

The Drug Abuse Warning Network (DAWN) database and FDA spontaneous reports were reviewed to evaluate abuse potential for the combination drug and for the individual components. The DAWN database uses the Annual Medical Examiner (ME) reporting system, which defines a drug abuse death as being either drug-induced or drug-related. A drug-induced death is any death in which the ME concluded that the fatality was caused directly by the drug. For this classification, the ME has found or strongly suspected a toxic level of drug in the victim. Typically fatalities from overdoses are classified as drug-induced. On the other hand, a drug-related death is a fatality in which the ME concluded that drug use contributed to the death but was not its sole cause. The term ME 'drug mention' refers to a substance or drug that is reported ("mentioned") in a drug abuse death report submitted to DAWN. The "raw" drug mentions presented in the Annual Reports do not represent the nation as a whole or even the total of ME drug abuse cases for a given reporting area. Instead these numbers reflect only those facilities that reported to DAWN during all or at least 10 months of a given reporting year.

Table 8 DAWN medical examiner drug mentions, raw (upper panel); and Consistent Panel listings of drug abuse deaths (lower panel)

	Mention Frequency by Reporting Year					
Substance	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**
Raw Data						
Acetaminophen	309	367	353	403	401	427
Aspirin	80	105	107	92	101	104
Ibuprofen	36	26	32	40	31	35
Pseudoephedrine	28	38	43	37	41	67
Total number of drug abuse cases	8,426	9,216	9,484	9,743	10,123	11,651
Consistent Panel Data						
Acetaminophen	---	---	342	392	395	425
Aspirin	---	---	103	87	98	104
Ibuprofen	---	---	NM†	NM	NM	NM
Pseudoephedrine	---	---	NM	NM	NM	NM
Total number of drug abuse cases	---	---	9,242	9,501	10,056	11,570

†NM signifies zero mentions.

In order to examine trends of drug abuse over time, a subset of the total ME facilities reporting drug abuse deaths for at least 10 months of a contiguous series of years is used. This subset of reporting MEs constitutes the Consistent Panel data. Data from the Consistent Panel permits detection of either new substances or new combinations of substances that result in drug abuse fatalities. For a given Annual Report, only four years of data are presented in the Consistent Panel data- the current year plus a three-year retrospective. This duration is chosen because, from one year to the next, different MEs contribute to the Consistent Panel.

Table 8 shows the numbers of drug mentions by medical examiners for acetaminophen, aspirin, ibuprofen and pseudoephedrine. The numbers of drug mentions for either ibuprofen or pseudoephedrine are much lower than for the other two. Also, there were no drug abuse deaths recorded by the Consistent Panel for ibuprofen or pseudoephedrine.

The DAWN database also lists reports on drug abuse episodes seen in Emergency Departments (ED) for a given year in 21 US metropolitan areas. An ED drug abuse episode or ED episode refers to any ED admission that was induced by or related to drug abuse. Drug abuse for the ED reports is defined as non-medical use of a substance for any of the following reasons: psychic effect, dependence, or suicide attempt/gesture. Non-medical use for purposes of the ED

Table 9 DAWN emergency department drug mentions [ISS p45/814]

	Mention Frequency by Reporting Year						
Substance	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**
Acetaminophen	38,674	36,563	38,265	35,448	32,257	28,258	33,613
Aspirin	19,358	16,729	15,854	14,623	15,457	12,815	15,657
Ibuprofen	9,031	21,250	16,979	17,070	17,146	14,400	17,923
Pseudoephedrine	2,377	1,956	1,362	1,793	1,355	598	948
Total	518,521	513,633	514,347	537,058	542,544	544,392	na

report series is meant as: the use of prescription drugs in a manner inconsistent with accepted medical practice; the use of over-the-counter drugs contrary to approved labeling; or the use of any substance for psychic effect, dependence, or suicide. The terms ED drug mention or ED mention refer to a substance that was mentioned in a drug abuse episode. Up to four substances can be reported for each ED episode.

Table 9 shows ED drug mentions for the years 1994-2000. ED drug mentions were much less frequent for ibuprofen and for pseudoephedrine than for acetaminophen, supporting a low abuse potential for the individual ingredients. Ibuprofen/pseudoephedrine combination products were not mentioned among the top 15 drugs in combination or the most frequent two-way drug combinations associated with ED visits.

MO Comment: Table 9 shows apparent trends with time. The total number of ED visits increased steadily throughout 1994-1999, but the numbers of aspirin, acetaminophen and pseudoephedrine drug mentions decreased, so that the proportion of ED visits in which these drugs were mentioned decreased in all three cases (for aspirin, from 3.7% to 2.3%; for acetaminophen, from 7.5% to 5.1%; for pseudoephedrine from 0.5% to 0.1%). Ibuprofen mentions, however, increased from 1.7% to 2.6% of ED visits in the same period, although the proportion of ibuprofen mentions peaked in 1995 at 4.1% of ED visits. Likewise, in the AAPCC data (Figure 5 and Table 6) ibuprofen poisoning reports increased from 1994 to 1999 although aspirin remained relatively steady and acetaminophen reports decreased. The AAPCC reports for ibuprofen did not peak in 1995 but increased over the report period.

FDA's Spontaneous Reporting System (SRS) database and the Adverse Event Reporting System (AERS) were searched for evidence of abuse involving pseudoephedrine, ibuprofen or ibuprofen/pseudoephedrine. For the SRS database, which contains spontaneous adverse drug experience (ADE) reports received by FDA from October 1969 to October 1997, the following COSTART coding terms were used in selecting adverse drug experience reports associated with drug abuse: DRUG DEPEND and DRUG DEPEND ADDICT. For the AERS database, which contains ADE reports beginning with November 1997 through the end of September 2000, the following MedDRA coding terms were used for report (ISR) selection: Abuse NOS, Drug Abuse, and Drug Dependence. After extraction of the individual report numbers, trade names associated with "suspect" drug names were converted to the generic equivalent and tabulated.

Table 10 shows the results of the search for spontaneous reports involving drug abuse. A total of 7,765 reports (0.52% of all SRS reports) in the SRS database were encoded with the COSTART search terms and a total of 1,572 initial reports (0.32% of all reports) in the AERS database were encoded with the MedRA search terms. For the cases reported in Table 10, the reported patient age was outside of the specified range (0 to <12 years of age) or else the age was not available. There were no abuse reports for the combination of pseudoephedrine and ibuprofen. These data support the finding that there is little abuse potential for pseudoephedrine and for ibuprofen.

Table 10 Drug abuse reports from SRS and AERS

	SRS Database		AERS Database[1]	
Substance Names	**Number of ISR found**	**% (of abuse reports)**	**Number of ISR found**	**% (of abuse reports)**
Acetaminophen-unspecified	3	0.04	1	0.06
Acetaminophen-Tylenol	5	0.06	2	0.12
Aspirin	5	0.06	0	0
Ibuprofen-Advil	3	0.04	0	0
Ibuprofen-Motrin	7	0.09	0	0
Ibuprofen-unspecified	1	0.01	0	0
Pseudoephedrine	2	0.03	0	0
Pseudoephedrine-Sudafed	5	0.06	0	0
Ibuprofen/Pseudo-ephedrine	0	0	0	0
Alprazolam	742	9.6	12	0.76
Tramadol HCl	296	3.81	92	5.85
Total Records (ISR) contained in database	1,486,926		498,733	

[1]Only reports noted as "initial" are included.

A report of pseudoephedrine abuse was found in the literature [Sullivan G: Acute psychosis following intravenous abuse of pseudoephedrine hydrochloride: a case report. J Psychopharmacol 1996;10(4): 324-325]. Three articles were identified describing pseudoephedrine hydrochloride overdose in subjects 2 to <12 years of age. All patients discussed in the articles recovered without serious sequelae.

Roberge RJ, Hirani KH, Rowland PL, Berkeley R, Krenzelok EP: Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. J Emerg Med, 1999; 17(2):285-288.

Wezorek C, Dean B, Krenzelok E: Pseudoephedrine: a prospective study to establish a toxic dose in children. Clin Toxicol 1995; 33(5): 554

Sauder KL, Brady WJ Jr, Hennes H: Visual hallucinations in a toddler: Accidental ingestion of a sympathomimetic Over-the-Counter nasal decongestant. Am J Emerg Med 1997; 15(5): 521-526

There were no reports of ibuprofen abuse in the age group 2 to <12 years of age. Four articles were identified for ibuprofen overdose in children 2 to <12 years of age, of which three discuss specific cases. In all three reports, subjects recovered without sequelae.

Kim J, Gazarian M, Verjee Z, Johnson D: Acute renal insufficiency in ibuprofen overdose. Ped Emerg Care 1995; 11(2): 107-108.

Al-Harbi NN, Domrongkitchaiporn S, Lireman DS: Hypocalcemia and hypomagnesemia after ibuprofen overdose. Ann Pharmacother 1997; 31: 432-434.

Zuckerman GB, Uy CC: Shock, metabolic acidosis, and coma following ibuprofen overdose in a child. Ann Pharmacother 1995; 29: 869-871.

There were no articles identified on abuse/overdose related to the above combination. The lack of literature supports the low abuse/addiction potential for the product.

D. Postmarketing Safety Surveillance

The first pediatric ibuprofen and pseudoephedrine combination suspension product was introduced for OTC marketing in September 2000. The ibuprofen and pseudoephedrine combination tablet was approved for OTC use by adults in 1989, and ———— tablets and caplets have been marketed since that time. The combination tablet is intended for subjects 12 years and over, but the possibility exists for unintended or inappropriate ingestion by children.

Serious reports from WHR and GSSE databases

The Sponsor provided a listing of serious cases for ibuprofen and pseudoephedrine combination products over the period 1989 – 2000 which corresponds to the initial marketing of the combination product. The complete listing is given in Appendix B. FDA's SRS postmarketing surveillance reports 1989--1997 were reported in COSTART terms, while FDA's AERS reports subsequent to that were reported in MedRA terms. Whitehall-Robins Healthcare spontaneous reports were identified as WHR-GSSE, denoting the change in reporting to the Wyeth-Ayerst (GSSE) division in May 2000.

Appendix B lists 56 serious cases reported to Whitehall-Robins Healthcare involving the combination product. There were 58 reports, but one case was listed three times, and two more cases may be duplicates (there may be only 54 distinct cases). There were 2 reports with concomitant ingestion of ibuprofen and pseudoephedrine hydrochloride. The majority of the reports were received from France, and the remainder were from the US. In many (16/56) of the reports only a single dose of the combination product was consumed.

Of the 58 reports, four were evaluated by the Sponsor as 'unrelated' in causality, ten as 'doubtful', five as 'possible' and three as 'probable' or 'related'. No assessment of causality was available in the remaining 36 cases. Only one report (98-0180-002), from France, was in a child, who became somnolent and experienced colic when her mother ingested an unknown amount of an ibuprofen/pseudoephedrine combination tablet and pneumorel for 4 days. No assessment of causality was included in the report. The remainder of the cases were in those aged 12 years or older, or else age was unknown.

A total of 21 cases had MeDRA Terms consistent with allergic reactions. Twelve of these 21 cases involved single doses or doses of only two tablets in a single day. In two cases the age was unknown, and one case occurred in a 16 year old:

98-0180-009 unknown Dermatitis NOS

99-0180-010 unknown Erythema multiforme Pruritus NOS Vascular purpura Rash pustular (history of urticaria, on concomitant medications)

00-0180-002 16 yo Edema NOS Pruritus NOS Dermatitis NOS Urticaria NOS (two tablets, single day, on concomitant medications)

In addition, five cases in adults involved angioneurotic edema:

MO Comment. In summary, the actual number of unique serious cases in the WHR-GSSE database was 55, since one case (99-0180-036) was listed three times, and two other cases, 95-0180-039 and 95-0180-019, involved the same event. Only one report was in a child, a one month-old, who experienced pain and somnolence when her mother ingested an unknown amount of an ibuprofen and pseudoephedrine combination tablet. Of the serious cases in adults, many

involved allergic reactions or angioneurotic edema. Several additional cases involved thrombocytopenia or agranulocytosis. These are all labeled adverse events for ibuprofen. There were three additional cases involving labeled adverse events for ibuprofen: one with melena and another with gastric hemorrhage, plus two cases of acute renal failure. There were several cases involving the cardiovascular or central nervous system. Most of the AEs listed in Appendix B have been described for either or both of ibuprofen and pseudoephedrine as single ingredients. In other cases confounding factors or incomplete data preclude definite conclusions regarding causality.

SRS and AERS serious reports

Appendix C shows 29 serious cases (all ages) from the FDA SRS and AERS databases for ibuprofen–pseudoephedrine combination products or for concomitant use of the single ingredient products, covering a time span of 1 January 1997 to 30 September 2000. Table 11 shows six serious cases involving both ingredients for subjects < 15 years old or age unknown.

Table 11. Serious cases (under 16 years old or age unknown) for ibuprofen+pseudoephedrine combination products or for concomitant use from FDA SRS (01/01/89–10/31/97) and AERS (11/01/97-9/30/00)

Age	Sex	Note	Dose	COSTART or MeDRA terms
	F	H*	1caplet/day unknown days	Paresthesia Vasodilatation Face edema Dyspnea NOS Cough Anaphylactoid reaction Drug interaction NOS Vomiting NOS
	F	I*	2 tablets od	Dysphagia Skin disorder NOS Pruritus Pain in limb Esophageal disorder NOS Edema upper limb Edema NOS Lack of spontaneous speech Dyspnea NOS Tongue disorder NOS Tongue edema Infection NOS
15 y	F	D, H†		Brain syndrome acute Edema brain Heart arrest NPN inc
5 y	M	H†	Sudafed 30 mg/day 54 days Ibuprofen 200mg 50 days	Allergic reaction Arthralgia Meningitis Rash
	F	H†	72 days	Atrial fibrillation
2 mo	M	H, I†		Accidental Overdose (therapeutic agent) Mental impairment NOS

*Combination product, †concomitant use. D death, H hospitalized, L life threatening, I intervention

MO Comment: Two pediatric cases are included above. One case involved a 5 year-old who received Sudafed, ibuprofen and acetylcysteine among other concomitant medications, and who experienced an 'allergic meningeal reaction', facial erythema, eyelid edema, and arthralgia. He was hospitalized and recovered. The second case was an overdose of acetaminophen, ibuprofen, pseudoephedrine, and calcium carbonate tablets in a two-month old child who recovered without sequelae.

Among the combination product users, two were of unknown age. Two concomitant users of single ingredient products were pediatric cases, one was a 15 year old, and one was age unknown.

Three of the cases in Table 11 are consistent with allergic reactions.

AERS reports for pediatric ibuprofen pseudoephedrine combination suspension

In response to an FDA request on October 18, 2001, the Sponsor searched the AERS database for adverse drug experiences (ADE) involving the pediatric ibuprofen and pseudoephedrine combination suspension product. The period searched in the AERS database was September 2000 through June 2001. A total of thirty-two non-serious ADE reports were identified, describing a total of fifty-two events, all of which identified the product as Children's Motrin® Cold (the only approved OTC combination suspension product containing ibuprofen and pseudoephedrine during the period searched).

There were no serious reports in this database. Eleven of the reports (34% of all reports) were encoded with MedDRA preferred terms suggesting a possible allergic reaction associated with product use.

	Children's Advil® Suspension Period Ending 6/26/00	Children's Advil® Suspension Period Ending 6/26/01	AERS reports for IBU/PSE Suspension 9/00 to 6/01
Patients with possible allergic events	25	24	11
Total number of patients reporting to AERS	106	105	32
% of patients with possible allergic events	**23%**	**23%**	**34%**

Table 12. Patients with possible allergic events, comparing pediatric ibuprofen suspension from annual safety reports, with ibuprofen/pseudoephedrine combination suspension reports from AERS

The sponsor reviewed the Annual Periodic Safety reports for NDA 20-589, Children's Advil® Suspension. This product was selected for evaluation over other ibuprofen containing products because: (a) the product is a suspension and is most similar in formulation to the marketed product; (b) the flavor and coloring systems are the most similar to the proposed product Children's Advil® Cold suspension (the Grape flavor of Children's Advil® is nearly identical to

	Count		
Event Term	**Children's Advil® Suspension Period Ending 6/26/00**	**Children's Advil® Suspension Period Ending 6/26/01**	**AERS reports for IBU/PSE Suspension 9/00 to 6/01**
Face oedema	11	12	6
Hypersensitivity NOS	5	3	0
Laryngeal oedema	0	1	0
Pruritis NOS	3	5	2
Rash pruritic	0	2	0
Urticaria NOS	13	14	6
Total Number of Allergic-type Events	**32**	**37**	**14**
Total Number of Events (Allergic and non-allergic)	**171**	**197**	**52**
% of Allergic-type events	**19%**	**19%**	**27%**

Table 13. Numbers of MeDRA terms possibly related to allergic events.

Children's Advil® Cold, with the exception of the active ingredient pseudoephedrine); and (c) the product is administered to children.

The following MedDRA terms were considered to be possible indications of an allergic reaction: Face oedema, Hypersensitivity NOS, Laryngeal oedema, Pruritis NOS, Rash pruritic, and Urticaria NOS. Table 12 presents the percent of patients reporting at least one of these reactions. Table 13 presents the percent of events possibly related to allergic events in 2

Age	Reactions	ISR Number
7YR	HALLUCINATION NOS, FACE OEDEMA	3624850
10YR	DERMATITIS NOS	3674390
3YR	PRURITUS NOS, URTICARIA NOS	3674392
5YR	FACE OEDEMA, URTICARIA NOS	3674393
35MN	FACE OEDEMA, PRURITUS NOS	3674394
5YR	DERMATITIS NOS, MOUTH ULCERATION	3674399
4YR	FACE OEDEMA	3674400
2YR	DERMATITIS NOS	3676067
3YR	DERMATITIS NOS	3728756
10YR	AGITATION, ABDOMINAL PAIN NOS, ASTHMA NOS, CHEST PAIN, MOVEMENT DISORDER NOS, VOMITING NOS, HALLUCINATION NOS, HEADACHE NOS	3728757
9YR	FACE OEDEMA	3728759
5.5YR	DERMATITIS NOS, URTICARIA NOS	3728760
3.5YR	URTICARIA NOS, DERMATITIS NOS	3728761
3.5YR	URTICARIA NOS	3728765
3.5YR	FACE OEDEMA, PARAESTHESIA, TREMOR, GAIT ABNORMAL NOS	3728766
5YR	URTICARIA NOS	3728770
14YR	DERMATITIS BULLOUS	3728771
32MN	EYE DISORDER NOS	3624848
13MN	VOMITING NOS	3624849
8YR	SEDATION	3674388
2YR	ACCIDENTAL OVERDOSE (THERAPEUTIC AGENT)	3674396
12YR	NERVOUSNESS	3674397
18MN	DRUG INEFFECTIVE	3674398
2YR	ACCIDENTAL OVERDOSE (THERAPEUTIC AGENT)	3676065
9YR	VOMITING NOS	3676068
4YR	DRUG INEFFECTIVE	3728758
36MN	VOMITING NOS	3728762
5.5YR	VOMITING NOS	3728763
5YR	DRUG INEFFECTIVE	3728764
4YR	RHINITIS NOS	3728767
10YR	ABDOMINAL PAIN NOS, VOMITING NOS	3728768
14MN	ATAXIA, SCREAMING, UNEVALUABLE REACTION	3728769

Table 14. Summary of 32 AERS reports for pediatric combination suspension product, September 2000 through June 2001

formulations (the total number of events is higher than the total number of patients because several events may have been reported by the same patient)

Table 14 .is a summary of the 32 AERS reports for the pediatric combination product. The first 17 reports in Table 14 may be consistent with allergic reactions including cases with MeDRA terms not identified by the Sponsor as indicating allergy (e.g., Asthma, Bullous Dermatitis).

MO Comment: Of the 17 AERS reports for the pediatric combination product that may have been consistent with allergic reactions, none was identified as serious. None of the cases occurred in a patient who reported a history of allergy to NSAIDS. Four of these subjects reported allergy histories: two to penicillin, one to amoxicillin, and one to grass. The number of allergic reactions to the pediatric product suggests a label warning not only to stop use, but also not to use any NSAID in the future if an allergic reaction occurs.

AERS and SRS reports for individual ingredients in pediatric subjects

The Sponsor's submission listed serious adverse event reports from the FDA SRS and AERS databases and from the sponsor's database in subjects of age 2 to 12 years, where drug products with either of the individual ingredients ibuprofen and pseudoephedrine were suspect drugs. The number of such serious reports is listed in Table 15.

Table 15 Serious cases, either ibuprofen or pseudoephedrine used in patients aged 2 to <12 years

Suspect Drug	SRS and AERS 9/19/89-09/30/01	WHR+GSSE 9/19/89-12/31/00
Ibuprofen	126	112
Pseudoephedrine	21	0

MO Comment The reviewer selected cases from the single ingredient serious AE listings (2 to <12 age group) in the submission that mostly involved the central nervous system for further investigation using the FDA SRS and AERS databases. These cases are shown in Table 16, which lists 20 reports. Of these, 8 involved ibuprofen without concomitant medications, including one death (that had no additional information), one allergic reaction (serum sickness) and one case of Reye's Syndrome. The table lists 5 additional cases involving ibuprofen and concomitant medications, including two more deaths, another allergic reaction and another instance of Reye's Syndrome. There was one report of hemiplegia, which involved an aortic valve abscess and vegetation in a patient who took ibuprofen; the hemiplegia may have resulted from an embolism. One report with a COSTART term of quadriplegia involved a patient who took ibuprofen but whose clinical picture was suggestive of viral encephalitis.

There was one overdose case involving pseudoephedrine without any concomitant drugs; this case resulted in convulsions and coma. In the six additional reports involving pseudoephedrine with concomitant drugs, there was one death following an allergic reaction and one overdose. There were two reports involving Triaminic, which can be a combination product containing dextromethorphan (explicitly noted in one report). Dextromethorphan may be

associated with dystonia (Drug Dex Evaluations). One of these reports involved a 10 year old with cerebral palsy who developed choreoathetosis. The other was a 3 year old who was reported by his mother to have paralysis with COSTART terms of anorexia, oculogyric crisis, paralysis, somnolence. This may have been a dystonic reaction, however further information was not available and causality is not clear.

Table 16 Serious pediatric cases, individual ingredients

Age	Drug	Concomitants	Event
8	Ibuprofen		Cholestatic jaundice, serum sickness-like reaction
6	Ibuprofen		Accidental overdose, metabolic acidosis, shock, coma
10	Ibuprofen		Hematoma on head from trauma, acute renal failure, convulsions, coma
2	Ibuprofen		Death
2.7	Ibuprofen		Endocarditis due to group A beta-hemolytic streptococcus after varicella; aortic valve abscess and vegetation, seizures and hemiplegia. CT scan revealed right-sided cerebral infarct
3	Ibuprofen		Varicella, convulsions
2	Ibuprofen		Ataxia, choreoathetosis, speech disorder
8	Ibuprofen		Reye's Syndrome.
3	Ibuprofen	amoxillin	Confusion, hostility and hallucinations
3	Ibuprofen	cefpodoxime	Otitis media, reporter hypothesized anaphylaxis, extracellular cerebral edema at autopsy
4	Ibuprofen	penicillin paracetamol	Hepatomegaly, encephalopathy, spastic quadriplegia, uncontrollable fits. Bilateral bright hippocampi in MRI scan. Clinical picture "most suggestive of" viral encephalitis
2.5	ibuprofen	Vantin	Cerebromeningeal edema, death
11	Ibuprofen	Prozac	Reye's Syndrome
7	Pseudoephedrine		Coma, convulsions, overdose
10	Pseudoephedrine	Triaminic DM/Chlor	Subject with cerebral palsy developed choreoathetosis
8	Pseudoephedrine	Mucomyst	Diplopia, gait abnormal, overdose
3	Pseudoephedrine	Zyrtec diphenhydramine	Allergic reaction, hepatic failure, death
6	Sudafed	suprax	Seizures, visual hallucinations
6	Pseudoephedrine	acetaminophen	Confusion, brain syndrome acute, physician felt it was a drug reaction to Sudafed
3	Triaminic	albuterol	Anorexia oculogyric crisis paralysis somnolence, reported by mother

E. Literature Survey

The Sponsor found no safety reports in the literature for use of ibuprofen and pseudoephedrine combination products or for concomitant use of these drugs in children 12 years or less in age. The databases searched were MEDLINE, EMBASE Alert, BIOSIS PREVIEWS, Derwent Drug File, Toxline, and SciSearch. For a search period beginning in 1996, which was the first year of OTC marketing for pediatric ibuprofen suspension, the Sponsor found safety reports in the literature for use of the individual ingredients in children of 12 years or less. These reports through year 2000 are summarized below.

There were 16 reports on ibuprofen. These included an actual use study sponsored by Whitehall-Robins (Children's Analgesic Medicine Project, CAMP) which enrolled 41,810 children (Ashraf et al. 1999). This was an open label, prospective study which compared ibuprofen suspension to acetaminophen suspension. A total of 14,281 children under 2 years of age took at least one dose of either drug, and the incidences of abdominal pain, insomnia, and hyperkinesia were all under 1% in this group for both treatments. Only the incidences of fever, vomiting, diarrhea, rhinitis, rash, and otitis media were above 1% in the children under 2 years of age for either drug. A total of 15,863 children of age from 2 years to 12 years took at least one dose of either drug, and the only adverse events with incidences above 1% for either treatment were rhinitis, pharyngitis and otitis media. There were no cases of anaphylaxis, Reye's syndrome, renal failure, GI bleeding/perforation or necrotizing fasciitis. There were 4 deaths which were evaluated as unrelated to study drugs (herpes encephalitis, sepsis, meduloblastoma, sudden infant death syndrome).

Lesko and Mitchell (1997) found no increased incidence of acute GI bleeding, acute renal failure, anaphylaxis, or Reye's Syndrome among hospitalized children treated with ibuprofen or acetaminophen. This was a randomized, double blind, acetaminophen-controlled trial that was part of a larger trial (the Boston Fever Study) of 83,915 children treated for febrile illnesses and randomly assigned to receive acetaminophen (12 mg/kg) or ibuprofen (two groups, 5 or 10 mg/kg) and followed for four weeks.

A prospective cohort study in 203 children (Duffy et al. 2000) with juvenile arthritis found increased incidences of CNS symptoms and GI symptoms, but the incidences did not differ significantly between ibuprofen and other NSAIDS. One abstract reported ibuprofen use to be a risk factor for necrotizing fasciitis in children with varicella. The remaining reports were case studies, including: 2 cases of ibuprofen allergies (Diaz-Jarra et al. 2001) and a report of vanishing bile duct syndrome after Stevens-Johnson syndrome (Srivastava et al. 1998); 3 overdoses (Al-Harbi et al. 1997; Earley et al. 2000; Oker et al. 2000); a report of acute nonoligouric renal failure (Schaller and Kaplan 1998), a report of acute interstitial nephritis (Primack et al. 1997) and three additional cases involving renal failures after ibuprofen use in children (Moghal et al. 1998). There was a report of pseudoporphyria after 12 months of use (Ryder and McDonagh 2000); a report of pyloric channel stricture judged to result from healing ulcers in a 12 year old with CF taking high dose ibuprofen (Bell et al. 1999); and a report of drug-induced immune thrombocytopenia (Bougie et al. 1998).

MO Comment: The literature reports are supportive of the safety of ibuprofen use in children. They also document the incidence of serious allergic reactions, renal failures, GI bleeds and thrombocytopenia which are labeled adverse events for prescription ibuprofen.

Al-Harbi NN, Domrongkitchaiporn S, Lirenman DS: Hypocalcemia and hypomagnesemia after ibuprofen overdose. Ann Pharmacother 1997; 31:432-434.

Ashraf E, Ford L, Geetha R, Cooper S: Safety profile of suspension in young children. Inflammopharmacology 1999; 7(3): 219-225.

Bell EA, Grothe r, Zivkovich V, Foote JM, Wellendorf J: Pyloric channel stricture secondary to high-dose ibuprofen therapy in a patient with cystic fibrosis. Ann Pharmacother 1999; 33:693-695.

Bougie D, Wilker PR, Curtis BR, Aster RH: Drug-induced immune thrombocytopenia induced by ibuprofen. Blood 1998; 10 (Pt 1, suppl 1): 180a.

Diaz Jara M, Perez Montero A, Garcia Bara, Cabrerizo S, Zapatero L, Martinez Molero MI: Allergic reactions due to ibuprofen in children. Ped Dermatol 2001;18(1): 66-67.

Duffy CM, Gibbon M, Yang H, Watanabe Duffy KN, Taylor G, Platt R:Non-steroidal anti-inflammatory drug-induced central nervous system toxicity in a practice-based cohort of children with juvenile arthritis. J Rheumatol 2000; 27 (Suppl 58):73(32)a.

Duffy CM, Gibbon M, Yang H, Watanabe Duffy KN, Taylor G, Platt R: Non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity in a practice-based cohort of children with juvenile arthritis. J Rheumatol 2000; 27 (Suppl 58):73(33)b.

Easley RB, Altemeier III WA: Central nervous system manifestations of an ibuprofen overdose reversed by naloxone. Ped Emer Care 2000; 16(1): 39-41.

Lesko SM, Mitchell AA: Renal function after short term ibuprofen use in infants and children. Pediatrics 1997; 100(6): 954-957.

Moghal NE, Hulton SA, Milford DV: Care in the use of ibuprofen as an antipyretic in children. Clin Nephrology 1998; 49(5):293-295.

Oker EE, Hemann L, Baum CR, Fentzke KM, Sigg T, Leiken JB: Serious toxicity in a young child due to ibuprofen. Acad Emer Med 2000; 7(7):821-823.

Primack WA, Rahman SM, Pullman J: Acute renal failure associated with amoxicillin and ibuprofen in an 11-year-old boy. Ped Nephrology 1997; 11(1):125-6.

Ryder CAJ, McDonagh JE: Pseuodoporphyria in a child treated with ibuprofen. J Rheumatol 2000; 27(suppl 58):92.

Schaller S and Kaplan BS: Acute nonoliguric renal failure in children associated with nonsteroidal antiinflammatory agents. Ped Emer Care 1998;14(6):416-418.

Srivastava M, Perez-Atayde A. Jonas MM: Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child. Gastroenterology 1998; 115: 743-746.

Zerr DM, Duchin JS, Rubens CE, Koutsky LA, Alexander ER: Ibuprofen as a risk factor for necrotizing fasciitis during primary varicella in children: A case control study. Abstracts of the IDSA 35th Annual Meeting. No. 33.

There were 6 reports on pseudoephedrine, including a prospective study to determine the toxic dose (Wezorek et al. 1995). This study examined 140 exposures in children under 6 years of age (mean age 2.5 years). There was one serious outcome in a 2 year old who ingested 600 mg and was hospitalized. Among subjects who ingested <180 mg, 21.7% experienced drowsiness and 6.9% experienced mild hyperactivity. Among those who ingested >180 mg, 15.4% experienced drowsiness and 12.8% experienced mild hyperactivity. Acute exposures of 180 mg and 11 mg/kg were well tolerated.

A clinical trial in 50 children (Buchanan et al. 1999) given oral pseudoephedrine or placebo for ear pain associated with air travel (1 mg/kg dose) reported significantly more drowsiness in the children given pseudoephedrine (30/50 flights) than in the placebo group (11/41 flights,

p=0.003). A pharmacokinetic study in 21 children aged 6 to 12 years (Simons et al. 1996) found a statistically significant increase in pulse rate 4 hours after a 60 mg dose of pseudoephedrine. There were three case reports, including one serious case (Sauder et al. 1997) with recurring visual hallucinations which resolved without sequelae and one allergic reaction to pseudoephedrine (Hindioglu et al. 1998).

These data support the safety of pseudoephedrine.

Buchanan BJ, Hoagland J, Fischer PR: Pseudoephedrine and air travel-associated ear pain in children. Arch Pediatr Adolesc Med 1999; 153:466-468.

Hindioglu U, Sahin S: Nonpigmenting solitary fixed drug eruption caused by pseudoephedrine hydrochloride. J Amer Acad Dermatol 1998; 38(3): 499-500.

Sauder KL, Brady WJ, Hennes H: Visual hallucination in a toddler: Accidental ingestion of a sympathomimetic over-the-counter nasal decongestant. Am J Emer Med 1997; 15:521- 526.

Simons FER, Gu X, Watson WTA, Simons KJ: Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children.1996; J Pediatrics 129(5): 729-734.

Soutullo CA, Cottingham EM, Keck PE Jr: Psychosis associated with pseudoephedrine and dextromethorphan [letter]. J Am Acad Child and Adolesc Psych 1998; 38(12): 1471-2.

Wezorek C, Dean B, Krenzelok E: A prospective study to establish a toxic dose in children. J Toxicol Clin Tox 1995; 33(S): 554.

VIII. Dosing Regimen and Administration Issues

The product can be used every 6 hours as needed up to a maximum of four times per day. The label also cautions against using more than the recommended dosage.

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

Table 17 Dosing table

MO Comment The Sponsor proposed a 3 day limit for fever or pain and a 7 day limit for cold, sinus and flu symptoms. Due to the limited exposure of subjects in the safety trial with fever and the limited number of subjects who used the drug for 7 days, there is insufficient data to support a 7 day duration of use for children.

IX. Conclusions and Recommendations

NDA 21-373 from Whitehall-Robins is an application for Children's Advil Cold (ibuprofen 100 mg/pseudoephedrine hydrochloride 15 mg per 5 mL) as a nonprescription drug for the temporary relief of the following cold, sinus and flu symptoms: nasal and sinus congestion, minor aches and pains, headache, sore throat and fever. The product is intended for use in children 2 years to under 12 years of age.

The supporting clinical trials to support approval included in this application are: two pharmacokinetic studies, AQ-99-02 and AQ-00- 04, and a safety study, AQ-99-03. The population in Study AQ-99-02 comprised children 6 to <12 years of age (n=29) and that of Study AQ-00-04 comprised children from 2 years to <6 years of age (n=23), for a total of 52 subjects. The safety study, AQ-99-03, included children from 2 years to <12 years (n=104 evaluable). The pharmacokinetic studies found that the absorption and elimination of the two components of the combination product are similar to those for the single ingredients given separately, without significant pharmacokinetic interaction.

The safety trial AQ-99-03 enrolled 106 subjects who used the combination drug for up to 7 days (up to 28 doses per subject). Of these, 29 subjects reported 38 AEs; none were serious. Most of the AEs were mild or moderate, and 12 of the 38 AEs were judged to be related to the medication. One subject discontinued because of an AE severity rated as moderate (subject felt shaky) and probably related to study medication. The results of this study are supportive of safety, however the study was limited to 7 days of follow-up.

When the safety study was combined with the two pharmacokinetic studies, there were 156 children who used the combination drug for up to seven days, with a favorable adverse event profile. The clinical trials in this application used a formulation with ibuprofen 110 mg and pseudoephedrine 15 ml per 5 mL of suspension. Following the NDA submission, it was agreed to market a slightly different formulation, with ibuprofen 100 mg and pseudoephedrine 15 mg per 5 mL of suspension, to avoid confusion in the marketplace. The FDA agreed that clinical data from pharmacological and safety studies using the ibuprofen 110mg/5 mL strength could be applied to the NDA formulation at 100 mg/5 mL.

The NDA also included summaries of worldwide postmarketing surveillance reports. Results were reviewed from a search of the American Association of Poison Control Centers (AAPCC) database, from the Drug Abuse Warning Network (DAWN) database and from the FDA spontaneous reporting system. About ~~~ were written for pediatric ibuprofen between 1989 and 1994. From the 1995 OTC approval of a pediatric ibuprofen suspension in the US through mid-1999, almost 50 million ounces of suspension have been sold (Ashraf et al. 1999), amounting to about ~~~ (for an assumed average of 10 mL per dose)

The AAPCC reports revealed the following trends in overdose and abuse patterns for ibuprofen and pseudoephedrine products:

- Poisonings in children aged 2 to <12 result predominantly from unintentional ingestion. However, during the entire period covered by the AAPCC reports, there were 3 deaths in the <12 year old age group, supporting the relative safety of ibuprofen and pseudoephedrine even in overdose. It is likely that an adult product was administered to children since a pediatric combination product became available only in 2000. Availability of pediatric ibuprofen/pseudoephedrine combination products may make this less of a problem. If this trend does not improve, revised labeling should be considered.
- Poisoning reports for ibuprofen in children aged 2 to <12 increased from 1994 through 1999 whereas those for pseudoephedrine were steady
- Poisonings in children 12 years or more involved intentional ingestion in about half of cases.
- The number of poison reports in the children <2 years is consistently about 40% of the number of reports for children 2 to <12 years old.

An increase in the number of ibuprofen overdoses, relative to those for acetaminophen or aspirin, is also apparent from the DAWN reports. However, it should be also be noted that the number of deaths reported to the AAPCC poison centers is lower for ibuprofen than either acetaminophen or aspirin.

FDA SRS and AERS reports and the Sponsor's safety database from 1989 through 2000 revealed that 20% to 40% of the serious cases involved allergic reactions or angioedema. More than 30% of the reports for the pediatric combination product reported from 6/00 to 6/01 involved allergic reactions.

Recommendation. *This application is approvable. The bioavailability of ibuprofen and pseudoephedrine in this combination product have been shown to be similar to those of the individual components and similar across the age groups studied. The safety study was supportive of safety for the pediatric combination product, and the post-marketing surveillance review did not reveal unexpected adverse events for the combination product. Ibuprofen has a relatively large margin of safety. The review of overdose data showed that these patterns are different in children younger than 12 years versus older subjects, and that in the younger age group the overdoses are mostly unintentional. Availability of pediatric ibuprofen and pseudoephedrine combination products may make overdoses in children less of a problem since adult products would not be used to treat children. In addition, the allergy-related adverse events suggest that the allergy warning for the class of NSAIDs needs improvement. Consideration should be given to changing the first bullet under the "Do not use" heading to "If the child has ever had an allergic reaction to any pain reliever, fever reducer or nasal decongestant". The Agency is also addressing the analgesic allergy warning through the OTC monograph process.*

Appendices

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Marketing History of the Ibuprofen/Pseudoephedrine Combination

Product Name	Rx or OTC	Dosage Strength/ Concentration	Dosing schedules	Age Range	Registration Date	Withdrawal Date	Reason
AUSTRIA: Advil Cold Tablets	OTC	Ibuprofen 200mg Pseudoephedrine 30mg	1 to 2 tablets to a maximum of 6 tablets in 24 hours	Adults and children over 12 years of age	2 Jan 2001	NA	
BULGARIA: Advil Cold	Rx	"	"	"	5 June 2000	NA	
CZECH REP. : Advil Cold	OTC	"	"	"	20 Sept 2000	NA	
HUNGARY: Advil Cold	OTC	"	"	"	27 July 2000	NA	
SLOVAK REP. : Advil Cold	OTC	"	"	"	12 Dec 2000	NA	
POLAND: Advil Cold	OTC	"	"	"	16 July 1999	NA	
UK: Advil Cold & Sinus	OTC	"	"	"	2 Feb 1996	August 2000	Discontinued for commercial reasons (product license still alive)
	OTC	"	"	"	1 July 1992	24 July 2000	Suspended because never marketed (product license still alive)
FRANCE: Rhinadvil	OTC	"	"	"	19 July 1991	On the market	
ARUBA: Advil Cold & Sinus Caplets	OTC	"	"	"	5/1991	N/A	
ARUBA: Advil Cold & Sinus Tablets	OTC	"	"	"	9/1994	"	
CURAÇAO: Advil Cold & Sinus Caplets	OTC	"	"	"	5/1991	"	
CURAÇAO: Advil Cold & Sinus Tablets	OTC	"	"	"	9/1994	"	
JAMAICA: Advil Cold & Sinus Caplets	OTC	"	"	"	6/1999	"	
JAMAICA: Advil Cold & Sinus Tablets	OTC	"	"	"	6/2000	"	
TRINIDAD: Advil Cold & Sinus Caplets	OTC	"	"	"	6/1991	"	
TRINIDAD: Advil Cold & Sinus Tablets	OTC	"	"	"	Currently in process	"	
GUYANA: Advil Cold & Sinus Caplets	OTC	"	"	"	Not registered		

Product Name	Rx or OTC	Dosage Strength/ Concentration	Dosing schedules	Age Range	Registration Date	Withdrawal Date	Reason
GUYANA: Advil Cold & Sinus Tablets	OTC	"	"	"	10/1999	N/A	
CANADA: Dristan Sinus Tablets	OTC	"	Single: 1-2 tabs. daily max. 6 tabs.	"	1993	N/A	
ARGENTINA: Ibudristan	Rx	"	1 capsule every 4-6 hours. Do not exceed 6 capsules in 24 hours	"	7/30/92	N/A	
COLOMBIA: Dristan Sinus Tablets	OTC	Ibuprofen 200 mg Pseudoephedrine 30 mg	1 tablet every 4-6 hours. Do not exceed 6 tablets in 24 hours	Adults and children over 12 years of age	May 8, 1995 (local manufactured) and January 20, 2000 for imported product	N/A	
BAHRAIN: Advil Cold & Sinus Caplets	Rx	"	1 or 2 caplets every 4 hours as needed. Do not exceed 6 caplets in 24 hours	Adults and children over 12. Do not give to children aged 2-12		N/A	
GHANA: Advil Cold & Sinus Caplets	Rx	"	"	"		N/A	
KUWAIT: Advil Cold & Sinus Caplets	Rx	"	"	"		N/A	

Product Name	Rx or OTC	Dosage Strength/ Concentration	Dosing schedules	Age Range	Registration Date	Withdrawal Date	Reason
LEBANON: Advil Cold & Sinus Caplets	Rx	Ibuprofen 200mg Pseudoephedrine 30 mg	1 or 2 caplets every 4 hours as needed. Do not exceed 6 caplets in 24 hours	Adults and children over 12. Do not give to children aged 2-12		N/A	
OMAN: Advil Cold & Sinus Caplets	Rx	"	"	"		N/A	
PALESTINE: Advil Cold & Sinus Caplets	Rx	"	"	"		N/A	
QATAR: Advil Cold & Sinus Caplets	Rx	"	"	"		N/A	
UAE: Advil Cold & Sinus Caplets	Rx	"	"	"		N/A	

Appendix B Serious Cases from WHR-GSSE (reproduced from the Sponsor's tables)

Serious cases from WHR-GSSE for ibuprofen and pseudoephedrine combination products, 01/01/1989 to 12/31/00. Listings are continued in following tables.

Report Number	Country and Source	Age (yrs)	Sex	Total Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
91-007C	US NHP	51	M	6 (?8) tabs/24hr	1 Dose(s)	Cold symptoms	Speech disorder NEC Cerebral ischemia Muscle twitching	H	N A
93-011A	US HP	45	F	1 tab	1 Dose(s)	Cold symptoms	Fibrillation atrial	H	Possibly related to pseudoephedrine component of the product.
94-0180-012	US NHP	48	F	4 caplets/day	10 Day(s)	Cold symptoms	Hemoglobin Thrombocytopenia	L, H	N A
94-0180-024	FRANCE HP	50	M	6 tabs/d	Use duration unknown	Cold symptoms	Mucous membrane disorder NOS	H	Not related
95-0180-001	U.S. NHP	45	M	Two caplets x 1	1 Dose(s)	Head cold scratchy throat	Pain NOS Vasodilatation	H, I	N A
95-0180-016	FRANCE HP	33	M	8 tabs, X1/day	1 Day(s)	Cold symptoms	Myocardial infarction	H	Not related
95-0180-019	FRANCE HP	-	F	1 cap 3x daily	1 Dose(s)	Influenza	Coma NEC	L, H	Not related
95-0180-039	FRANCE HP	57	F	3 tablets	1 Day(s)	Influenza and sinusitis	Convulsions NOS Stupor	L, H	N A
95-0185-003	US HP	17	F	8 tablets	1 Dose(s)	Intentional overdose	Non-accidental overdose	H, O	Related
95-0530-001	US NHP	46	F	2 caplets	1 Dose(s)	Unknown	Hypersensitivity NOS Dyspnea NOS Hypotension NOS	H	N A
96-0180-018	FRANCE HP	21	F	Unknown	10 Day(s)	Tonsilitis	Pruritus NOS Rash papular	H	N A

N A, Not available H, Hospitalized I, Intervention L, Life Threatening O, Other NOS, Not otherwise specified A, Disability, D Death.

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Serious cases from WHR-GSSE, continued.

Report Number	Country and Source	Age (yrs)	Sex	Total Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
98-0180-002	FRANCE HP	0.08	F	Unknown	4 Day(s)	Unknown	Pain NOS Somnolence	H	N A
98-0180-006	FRANCE HP	15	M	Unknown	Unknown	Unknown	Idiopathic thrombocytopenic purpura	H	"Doubtful link between the event and product use"
98-0180-007	FRANCE HP	61	F	3 tablets qd	1 Dose(s)	Acute nasopharyn -gitis	Edema NOS Pyrexia Rash papular	H	The events are believed to be related to product use.
98-0180-009	FRANCE HP	-	U	Unknown	Unknown	Unknown	Dermatitis NOS	H	"Doubtful link between the event and product use"
98-0180-010	FRANCE HP	35	M	2 tablets bid	6 Day(s)	Unknown	Peripheral vascular disease NOS	H	"A possible link between the product use and the event"
98-0180-013	FRANCE HP	63	F	Unknown	4 Day(s)	Unknown	Dysarthria Gastritis NOS Gastric hemorrhage	H	N/A
98-0180-015	FRANCE HP	-	F	3 tablets qd	1 Week(s)	Unknown	Diplopia	A	N/A
98-0180-019	FRANCE HP	-	F	Unknown	Unknown	Rhinitis	Renal failure acute Hepatic necrosis Dermatitis Disseminated intravascular coagulation Sepsis NOS Thrombocytopenia Hemorrhagic stroke	D, H	No link between product use and the events.

Report Number	Country and Source	Age (yrs)	Sex	Total Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
96-0180-027	FRANCE HP	49	F	1 tab	1 Dose(s)	Acute Rhinitis	Asthma NOS	L, H, I	N/A
96-0180-037	US NHP	53	M	2 tabs qd	2 Day(s)	Cold	Dizziness (exc vertigo) Melena	H, I	N/A
96-0185-008	FRANCE HP	38	F	1 tab	1 Dose(s)	Sore throat	Angioneurotic edema Dermatitis NOS	H, O	N/A
96-0185-010	FRANCE HP	25	F	2 tabs	1 Dose(s)	Rhinitis	Convulsions NOS	H, I, O	N/A
96-0575-001	US NHP	73	M	1 tab	1 Dose(s)	Runny nose & sore throat	Hypersensitivity NOS	H	N/A
97-0180-005	FRANCE HP	23	F	400mg/60mg qd	24 Day(s)	Rhino-pharyngitis	Gingival bleeding Thrombocytopenia	H	N/A
97-0180-010	US NHP	50	F	2 tablets qd	1 Dose(s)	Cold	Dyspnea NOS Face edema Eye disorder NOS Glossitis Pain NOS	I	N/A
97-0185-006	FRANCE NHP	52	M	unknown	Unknown	Allergic Rhinitis	Angina pectoris	H	N/A
97-0185-008	FRANCE HP	-	M	unknown	5 Day(s)	Unknown	Arterial spasm NOS Hemiplegia	H	N/A
97-1265-003	US NHP	60	F	1 tab	1 Dose(s)	Sinus Headache	Hypersensitivity NOS Tongue edema Laryngospasm Chest pain NEC Dermatitis NOS	H	N/A

Serious cases from WHR-GSSE, continued.

Report Number	Country and Source	Age (yrs)	Sex	Total Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
98-0180-020	FRANCE HP	42	M	3 tabs qd	2 Day(s)	Rhinitis and pharyngitis	Urticaria NOS	I	N A
98-0180-022	FRANCE HP	60	M	Unknown	Unknown	Unknown	Angioneurotic edema	H	N A
98-0180-023	FRANCE HP	21	F	1 tablet tid	2 Day(s)	Acute rhinitis and pharyngitis	Rash papular	H	Doubtful link between product use and the event
98-0180-033	FRANCE HP	45	F	3 tablets/day	7 Day(s)	Rhinitis	Rash papular	H	Doubtful link between product use and the event
99-0180-004	FRANCE NHP	59	M	1	1 Dose(s)	Unknown	Angioneurotic edema	H	N A
99-0180-005	FRANCE HP	54	F	2 tablets qd	7 Day(s)	Sore throat and ear pain	Face edema Pruritus NOS Rash papular Syncope	H	Possible link between product use and the events.
99-0180-009	FRANCE NHP	27	F	2 tabs	1 Day(s)	Unknown	Angioneurotic edema	H	Doubtful link between product use and the event.
99-0180-010	FRANCE HP	-	U	Unknown	4 Day(s)	Fever and cough	Erythema multiforme Pruritus NOS Vascular purpura Rash pustular	H	A likely link between product use and the events
99-0180-013	FRANCE HP	31	M	1 tablet	1 Dose(s)	Unknown	Face edema Urticaria NOS	H	Doubtful link between product use and the events.
99-0180-020	FRANCE HP	33	M	3 qd	5 Day(s)	Rhino-pharyngeal episode	Renal failure acute Nephritis NOS	H	N A

Report Number	Country and Source	Age (yrs)	Sex	Total Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
99-0180-021	FRANCE HP	48	F	3 tabs qd	8 Day(s)	Unknown	Vascular purpura	H	Doubtful link between product use and the event
99-0180-023	FRANCE HP	39	F	1 dose	1 Dose(s)	acute bronchitis	Malaise Tachycardia NOS	H	N A
99-0180-027	FRANCE HP	36	F	1 dose	2 Day(s)	Unknown	Bradycardia NOS Dizziness (exc vertigo) Dyspepsia Pruritus NOS Acute circulatory failure Urticaria NOS	L	Possible link between product use and the events
99-0180-033	FRANCE HP	18	M	Unknown	Unknown	Rhino-pharyngitis	Idiopathic thrombocytopenic purpura	H	Doubtful link between product use and the event
99-0180-036	FRANCE HP	27	F	Unknown	3 Day(s)	Rhinitis	Pruritus NOS Dermatitis NOS Rash papular	H	N A
99-0180-036	FRANCE NHP	27	F	3 qd	4 Day(s)	Rhinitis	Pyrexia Dermatitis NOS	H	N A
99-0180-036	FRANCE HP	27	F	3 tabs/day	4 Day(s)	Rhinitis	Pyrexia Pruritus NOS Dermatitis NOS Rash papular	H	Doubtful link between product use and the event.
99-0185-007	FRANCE HP	18	M	Unknown	5 Day(s)	Rhino-pharyngitis	Asthenia Thrombocytopenia	H	N A

Serious cases from WHR-GSSE, continued.

Report Number	Country and Source	Age (yrs)	Sex	Total Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
00-0180-002	FRANCE HP	16	F	2 tabs	1 Day(s)	Headache	Edema NOS Pruritus NOS Dermatitis NOS Urticaria NOS	H	N A
00-0180-009	FRANCE HP	32	F	Unknown	1 Day(s)	Influenza	Angioneurotic edema	H	N A
00-0180-010	FRANCE HP	36	M	1 tab	1 Day(s)	Rhino-pharyngitis	Anaphylactic reaction	L, H	N A
00-0180-012	FRANCE HP	52	F	3 tabs	2 Day(s)	Rhino-pharyngitis	Pruritus NOS Dermatitis NOS Rash papular	H	"Possibly related to NSAIDs"
00-0185-006	FRANCE HP	34	F	1 tablet bid	2 dose(s)	Unknown	Anaphylactic reaction Diarrhea NOS Vomiting NOS	H	N A
HQ284872 7OCT2000	France Regulatory Authority HP	22	U	3 Tablets	6 days	Unknown	Dysuria Asthenia Loss of consciousness NEC Malaise Neck Stiffness Rash *morbilliform*	H	N A
HQ297243 1OCT200	France Regulatory Authority HP	37	M	2 Tablets	7 days	Unknown	Agranulocytosis	H	Doubtful link between the event and product use

Report Number	Country and Source	Age (yrs)	Sex	Total Daily Dose	Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
HQ514222 1DEC2000	France, HP	37	M	400 mg daily	6 days	Sore throat NOS	Agranulocytosis Pyrexia Aspartate aminotransferase increased Alanine aminotransferase increased Gamma-glutamyltransferase increased	L	N A
HQ917823 1JUL2000	France Regulatory Authority HP	36	M	2 tablets	1 day	Pharyngitis NOS	Hypotension NOS Dyspnea NOS Face edema	Other medically important condition	N/A

N/A. Not available H, Hospitalized I, Intervention L, Life Threatening O, Other NOS, Not otherwise specified A, Disability, D Death.

Report Number	Country and Source	Age (yrs)	Sex	Medication, Daily Dose/Duration of Use	Indication	MedDRA Term	Outcome	Assessment of Casual Relationship
97-0150-040	France HP	21	F	Advil- dose unknown X 5 days Sudafed-dose unknown	Unknown	Aplastic anemia Purpura NOS Mucous membrane disorder NOS	H	N A
88-083	U S HP	15	F	400 mg Advil-1 dose Sudafed-amount unknown X 2 doses	Advil-ankle pain, Sudafed-nasal congestion	Cerebral edema	H, D	N/A

Note:
No serious reports associated with concomitant use of ibuprofen-containing product with pseudoephedrine-containing product for patients of age 2<12 years or of unknown age were identified in WHR+GSSE database.

Appendix C Serious cases from FDA AERS and SRS databases

Serious cases for ibuprofen+pseudoephedrine combination products or for concomitant use from FDA SRS (01/01/89–10/31/97) and AERS (11/01/97-9/30/00)

Age	Sex	Note	Dose	COSTART or MeDRA terms
30 y	F	H*		Syncope Hyperventilation Convulsion Anxiety
48 y	F	H, L*	4 tb/day unknown days	Thrombocytopenia Hemorrhage
32 y	F	H, I*		Purpura Thrombopenic Eosinophilia
	F	H*	1caplet/day unknown days	Paresthesia Vasodilatation Face edema Dyspnea NOS Cough Anaphylactoid reaction Drug interaction NOS Vomiting NOS
	F	I*	2 tablets od	Dysphagia Skin disorder NOS Pruritus Pain in limb Esophageal disorder NOS Edema upper limb Edema NOS Lack of spontaneous speech Dyspnea NOS Tongue disorder NOS Tongue edema Infection NOS
39 y	F	H*	1 dose	Anxiety Malaise Sinus tachycardia
49 y	F	L*	2 caplets bid unknown days	Pruritus Hypersensitivity NOS Syncope Throat edema Urticaria NOS Feeling jittery Myocardial infarction Vision blurred Accidental overdose (Therapeutic agent) Sedation Face edema Anaphylactic shock Collapse Dizziness (Exc Vertigo) Drug level NOS Dyspnea NOS Electrocardiogram abnormal NOS
36 y	F	H, L*	2 days	Vertigo Nec Abdominal pain Upper bradycardia NOS Dyspepsia Hypotension Pruritus Urticaria NOS
36 y	M	L*	1 day	Dyspnea NOS Face edema Arterial pressure NOS decreased
60 y	M	H, D*		Gastrointestinal Hemorrhage NOS Intestinal ulcer Rhinitis NOS
60 y	M	D*	3/day, 6 days	Hemorrhage NOS Gastrointestinal Hemorrhage NOS Intestinal ulcer
35 y	F	H, I*		Accidental overdose (therapeutic agent) Depressed level of consciousness
35y	F	I*	1 tablet	Dermatitis Atopic Hypersensitivity NOS Palpitations Pruritus
	F	H*	73 days	Atrial fibrillation Sinusitis NOS Tachycardia NOS
15 y	F	D, H†		Brain syndrome acute Edema brain Heart arrest NPN inc
19 y	F	H†	1 day	Overdose intentional
68 y	F	H†		Gastritis Hematemesis Melena
71 y	M	H†	Sudafed 2 tb/day 3 days, Advil unknown	Hypertonia No drug effect Syncope
36 y	F	H†		Syncope
5 y	M	H†	Sudafed 30 mg/day 54 days Ibuprofen 200mg 50 days	Allergic reaction Arthralgia Meningitis Rash

40 y	F	H†		Arrhythmia Coma Diabetes insipidus Overdose intentional
36 y	F	H†		Agranulocytosis LE syndrome Pain Stomatitis
21 y	F	H†	6 days	Fever Infect super Marrow Depression Pancytopenia Cough increase Pharyngitis (also on amoxicillin, hep B vaccine)
42 y	F	H†	1 day	Bronchospasm NOS Uterine fibroids Urticaria NOS Tachycardia NOS Anxiety Nec Serotonin syndrome Ovarian cyst Polyuria Arrhythmia NOS Panic disorder Nec Chest pain Drug interaction NOS Fatigue Flushing Hypersensitivity NOS Influenza like illness Intermenstrual bleeding Mouth ulceration Muscle cramps Myoclonic jerks
36 y	M	H†	22.4 g ibuprofen 12 tablets pseudo-ephedrine	Vomiting NOS Hyperkalemia Hypoventilation Mydriasis Myoglobinuria Overdose NOS Respiratory rate increased Sedation Convulsions NOS Tachycardia NOS Acidosis NOS Electrocardiogram ST Segment Depression Electrocardiogram T Wave Inversion Blood creatine phosphokinase increased
	F	H†	72 days	Atrial fibrillation
21 y	F	H, I†		Accidental overdose (therapeutic agent) Mental impairment NOS
42 y	M	H†		Aplastic Anemia Mucous membrane disorder NOS Purpura NOS
2 mo	M	H, I†		Accidental Overdose (therapeutic agent) Mental impairment NOS

*Combination product, †concomitant use. D death, H hospitalized, L life threatening, I intervention

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/s/

Linda Hu
4/9/02 03:06:26 PM
MEDICAL OFFICER

Linda Katz
4/9/02 03:30:59 PM
MEDICAL OFFICER

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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

NDA Number:	021373	**Trade Name:**	CHILDREN'S ADVIL COLD SUSPENSION(IBUPROF
Supplement Number:	000	**Generic Name:**	IBUPROFEN/PSEUDOEPHEDRINE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	ANALGESIC/ANTIPYRETIC/NASAL DECONGESTANT
Original NDA Action Date:	6/18/01		

Indication # 1 temporarily relieves symptoms associated with the common cold, flu, and sinusitis, including nasal congestion, fever, headache and minor body aches and pains, in children 2 to 11 years of age

Comments (if any):

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	2 years	Waived	

Comments: Studies of this product are waived in the 0-2 year age group because of the difficulty in diagnosing the cause of these symptoms in young children and the safety concerns of the use of this product without the consultation of a learned intermediary.

2 years	11 years	Completed	
12 years	18 years	Waived	

Comments: This product does not need to be studied in the ages of 12 to 18 years because there are existing ibuprofen/pseudoephedrine combination products approved and more appropriate for this age group.

This page was last edited on 4/12/02

1ST

Signature

4/12/02

Date

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