CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-587

MEDICAL REVIEW(S)

OTC Medical Team Leader Review

NDA 21-587
Drug : Ibuprofen 100 mg/5 ml, Pseudoephedrine HCl 15 mg/5 ml, Chlorpheniramine maleate 1 mg/5 ml
Dosage Form: Liquid Suspension
Proprietary Names: Children's Advil® Allergy Sinus [redacted]

Sponsor: Wyeth Consumer Healthcare
Pharmacologic Category: Internal Analgesic/Decongestant/Antihistamine
Proposed Indication: Temporarily relieves symptoms associated with hay fever or other respiratory allergies, and the common cold.
Submission Dates: April 23, 2003, August 22, 2003, August 28, 2003
Review Date: February 11, 2004
Reviewer Name: Andrea Leonard-Segal, M.D., M.S.

Recommendations:

- NDA 21-587 should be approved for the temporary relief of symptoms associated with hay fever or other respiratory allergies, and the common cold for children 6 to < 12 years of age, provided that:
  - the final printed labeling submitted by the sponsor is correct, and
  - there are no outstanding chemistry issues

- The proprietary names should be Children's Advil Allergy Sinus [redacted] [redacted]

- As a Phase IV commitment, the sponsor should provide data that clarifies whether consumers understand the difference between Wyeth's pediatric single ingredient and combination Advil [redacted] products based upon the information provided on the principal display panel.

Discussion:
This triple combination suspension contains three individual ingredients (ibuprofen, pseudoephedrine HCl, and chlorpheniramine) that are each approved and sold over-the-counter (OTC) as single ingredients for children and adults. These ingredients are also approved for OTC sale in combination with each other (ibuprofen plus pseudoephedrine, pseudoephedrine plus chlorpheniramine). NDA 21-441, a triple combination tablet containing ibuprofen 200 mg/ pseudoephedrine 30 mg/ chlorpheniramine 2 mg was approved on December 19, 2002 under the name Advil Allergy Sinus. The efficacy data from that NDA plus data from two pharmacokinetic studies submitted with NDA 21-587 were used to demonstrate the efficacy of the suspension. The indications for the tablet and suspension formulations are the same. The safety data submitted suggests that this triple combination product would be safe to use as directed in the OTC setting.

As of the time of this Medical Team Leader review, there are two outstanding review issues. The Chemistry review is not yet available and the final printed labeling needs to be evaluated.

If approved, this product will add yet another analgesic, decongestant, antihistamine combination product to the vast array already sold OTC to consumers. It is important to avoid consumer confusion about what ingredients are contained in combination products because such confusion could present safety and efficacy issues for the purchaser. Consumers should be able to distinguish among products that contain one, two, or three ingredients so they select the proper product for their medical condition and do not take more medication than they need. The sponsor should provide information about how well consumers can distinguish the different permutations of Wyeth's Advil . —— ——— products from each other. If Wyeth does not already have this data, they should conduct a study that will generate it and submit it as a Phase IV commitment.

Efficacy:
There were no efficacy studies submitted as part of this NDA. Efficacy for the pediatric population was extrapolated from the adult efficacy data provided in NDA 21-441, an approved triple combination tablet containing ibuprofen 200 mg, pseudoephedrine HCl 30 mg and chlorpheniramine 2 mg. Two pharmacokinetics studies following single dose administration of the triple combination suspension to healthy adults as well as to allergic children aged 6 to less than 12 years of age demonstrated that the rate and extent of absorption of the three ingredients were:

- similar to rate and extent of absorption of the triple combination tablet ingredients
- similar between children and adults

The indications and dosing directions for the triple combination suspension are consistent with those previously approved for OTC ibuprofen, pseudoephedrine, and chlorpheniramine in the target pediatric population.

Safety:
Safety data for this NDA was derived from:

- A pivotal safety study (AR-00-04),
- Two pharmacokinetic studies (AR-00-02 and AR-00-03),
- Post-marketing surveillance data (Wyeth Consumer Healthcare and FDA AERS)
- A review of worldwide literature (1/1/2000 – 10/15/2001)
- Reports from the American Association of Poison Control Centers (1995 – 2001)
- Reports from the Drug Abuse Warning Network (1994 – 2000)
- Emergency Department Reports (1994 – 2001)
- Four-month safety update

The data supports the safety of the triple combination suspension in children. No safety concerns beyond what is already known about each of the active ingredients in the product were noted.

In study AR-00-04, children 6 to 12 years old took the study drug every 6 hours, 3 times daily for 7 days. The most common adverse event was somnolence. The monograph (chlorpheniramine and pseudoephedrine HCl) and OTC NDA (ibuprofen) approved maximum daily dosing schedule for each active ingredient in the triple combination suspension is four times daily; this is the dosing schedule the sponsor has requested. In a perfect world, the sponsor would have studied the suspension with four times per day dosing in children, but they did not. However, considering our vast post-marketing experience with these ingredients at four times per day dosing in children, the safety profile presented in this study is sufficient to suggest that the suspension would be safe if dosed four times per day.

Chemistry
The chemistry review is not available at this time.

Pharmacology and Biopharmaceutics
The reviewers state that the application is acceptable. The sponsor tightened the dissolution specification to Q = [redacted] in 10 minutes to ensure lot-to-lot uniformity of the drug product, as per the Agency's request.

Pharmacology and Toxicology
Given that the clinical pharmacokinetic data showed no drug-drug interactions, the safety profile of each active ingredient is well established and the doses proposed are within those of currently marketed products, the Agency did not request non-clinical studies.

Labeling
At this time the Agency awaits submission of the sponsor's final printed labeling for the Advil and the [redacted] trade name triple combination products.

The sponsor proposed dropping the term "Sinus" from the Advil proprietary name for this product, thus changing the name to [redacted] The Division of Medication Errors and Technical Support (HFD-420) did not agree with this proposal because the new name might not be informative enough about the product.

Andrea Leonard-Segal, M.D., M.S.
Medical Team Leader
Division of Over-the-Counter Drug Products

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

/s/

Andrea Segal
2/12/04 09:58:23 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

OTC MEDICAL OFFICER'S REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

NDA #:	**21-587 (IND 63,999)**
Drug name:	**Ibuprofen 100mg/ 5 ml** **Pseudoephedrine HCl 15 mg/ 5 ml** **Chlorpheniramine maleate 1 mg/ 5 ml**
Trade Name:	**Children's Advil® Allergy Sinus**
Sponsor:	**Wyeth Consumer Healthcare**
Pharmacologic Category:	**Analgesic/Decongestant/Antihistamine**
Proposed Indications:	**Temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold**
Dosage Form:	**Suspension**
Route of Administration:	**Oral**
Submission Dates:	**April 23, 2003** **August 22, 2003** **August 28, 2003**
Review Date:	**November 14, 2003**
Reviewer:	**Daiva Shetty, MD**

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS:

EXECUTIVE SUMMARY:

I. RECOMMENDATIONS

A. Recommendations on Approvability

From a clinical perspective, the proposed ibuprofen 100 mg/pseudoephedrine 15 mg/chlorpheniramine 1 mg suspension is recommended for approval for the temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold for children 6 to < 12 years of age.

B. Recommendations on Phase 4 Studies and Risk Management Steps

No specific new post-marketing studies are needed.

C. The proposed label should be modified in the following ways:

- The principal display panel of the package should clearly identify all three ingredients and a statement of their identity. Listing of the active ingredients should be in a contrasted color from the background, and in a font size that is one half as large as the size of the trade name.
- The label should carry one additional warning: Ask a doctor before use, if the child has not been drinking fluids or lost a lot of fluids due to continued vomiting or diarrhea.

- Dosing directions should be changed from "do not use more than 4 times a day" to [redacted].

II. SUMMARY OF CLINICAL FINDINGS

A. Brief Review of Clinical Program

The proposed new combination product Children's Advil® Allergy Sinus / [redacted] suspension contains three active ingredients: ibuprofen (IBU), pseudoephedrine (PSE), and chlorpheniramine (CHLOR). Each 5 ml of suspension contains 100 mg of ibuprofen, 15 mg of pseudoephedrine hydrochloride, and 1 mg of chlorpheniramine maleate. The sponsor is proposing to market this product for children ages 6 to < 12 years old for temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold at the proposed dosing regimen of 10 ml every 6 hours not to exceed 4 doses a day.

This review is a safety review of the use of ibuprofen/pseudoephedrine/chlorpheniramine as single ingredients as well as in combination for children 6 to < 12 years of age.

The clinical development program in support of this NDA consists of:

1. Three clinical studies with the Children's Advil Allergy Sinus Suspension:
- AR-00-04 multiple dose safety study in children 6 to < 12 years of age,
- AR-00-02 bioequivalence and food-effects study in healthy adults, and
- AR-00-03 bioavailability study in children 6 to < 12 years of age.

2. Safety data concerning the combination and the single ingredients from:
- Postmarketing surveillance data from the Wyeth Consumer Healthcare (WCH) database (1/1/2001-4/30/2003) and from the FDA Adverse Event Reporting System (AERS) database (4/1/2001 - 6/30/2002),
- American Association of Poison Control Centers (AAPCC)(1995-2002),
- Drug Abuse Warning Network (1994-2001),
- Emergency Department Reports (1994-2002), and
- Worldwide literature discussing IBU and PSE (1/1/2000 - 7/1/2003), and CHLOR (all literature up to 7/1/2003) from a search of the MEDLINE, EMBASE Alert, BIOSIS REVIEWS, Derwent Drug File, Toxline, and SciSearch databases.

B. Efficacy

The proposed dosing directions for the new triple combination are consistent with the previously approved dosing regimens of the three single ingredients for the proposed target population. There were no efficacy studies in this NDA. Efficacy for the proposed pediatric population was extrapolated from the adult efficacy data for the triple combination tablet containing IBU 200 mg/PSE 30 mg/CHLOR 2 mg (NDA 21-441). The sponsor provided studies to demonstrate that this new liquid formulation is bioequivalent to the already approved tablet formulation for adults.

C. Safety

Data gathered from the pivotal safety study of AR-00-04, supports the safety of the new formulation when used three times a day for 7 days for upper respiratory allergies in the

proposed pediatric age category. This was a multicenter, open label, multiple dose safety study in children 6 to < 12 years of age suffering from upper respiratory allergies. A total of 111 subjects were enrolled and 110 completed the study. Subjects were instructed to take study medication every six hours, three times a day for seven consecutive days. There was relatively good compliance with the dosing directions. Overall, the AEs noted during the study # AR-00-04 are consistent with the previously known safety profile of the three active ingredients contained in the new combination, and with the AE profile in the clinical trial of the same combination drug in adults (Study # AD-99-02). There were no unexpected AEs noted in this trial. There were a total of 66 AEs reported by 39 (35%) pediatric subjects. The most common adverse event in children was somnolence, 13 (12%), which in most cases resolved within two days after study drug was taken. Only two subjects reported experiencing somnolence for longer than two days after receiving the first dose of the study medication. Other frequently occurring AEs included asthenia (n=9, 8%), headache (n=6, 5%), and abdominal pain (5, 5%). Three severe AEs were judged by the Investigator to be definitely, probably or possibly related to study drug: somnolence (n=1) and asthenia (n=2). In the adult trial AD-99-02 (NDA 21-441), the incidence of somnolence with the same dose of the product (IBU 200 mg/PSE 30 mg/CHLOR 2 mg) was 9.1%, and with the double dose 16.4% (IBU 400 mg/PSE 60 mg/CHLOR 4 mg) . The lower dose (IBU 200 mg/PSE 30 mg/CHLOR 2 mg) of the drug was approved for adults because of clear dose response effects for AEs.

Two pharmacokinetic studies (AR-00-02 and AR-00-03) enrolled a relatively small patient population. The extent of exposure to the drug was also limited. There were no unexpected or serious adverse events reported during the course of the two studies.

No new serious safety issues related to the labeled use of the proposed combination drug were uncovered during this review of the spontaneous AE reports contained in either the sponsor's internal AE database or the FDA database.

The worldwide literature review of data on safety of the three ingredients contained in the triple combination did not reveal any new serious safety concerns.

Reports from the American Association of Poison Control Centers and the Drug Abuse Warning Network do not suggest that the proposed combination product would have a potential for drug abuse.

D. Dosing
The frequency of dosing as proposed is:
For children 6 to 11 years (48 to 95 lbs) of age: take 2 teaspoons every 6 hours while symptoms persist, not to exceed more than 4 doses a day.

However, the safety of the new combination product in the proposed pediatric population was evaluated when used up to a maximum of ____ a day. Therefore, dosing directions should be revised to state: "...take 2 teaspoons every 6 hours while symptoms persist, not to exceed more [redacted]

The product is not to be taken for nasal congestion for more than 7 days or for pain or fever for more than 3 days.

E. Special Populations
The precautions for special populations, such as patients with underlying medical conditions or those who take concomitant medications, are appropriately conveyed by the label. Those warnings are consistent with other OTC medications containing ibuprofen, pseudoephedrine, and chlorpheniramine.

One additional warning is recommended for the use of the proposed product by children with dehydration: Ask a doctor before use if the child has not been drinking fluids or lost a lot of fluid due to continued vomiting or diarrhea.

CLINICAL REVIEW:

I. Introduction and Background

This is a clinical review of a New Drug Application for a new pediatric combination drug product to be marketed under two names: Children's Advil® Allergy Sinus and [redacted] Each 5 ml of suspension contains 100 mg of ibuprofen, 15 mg of pseudoephedrine hydrochloride, and 1 mg of chlorpheniramine maleate. The sponsor is proposing to market this product for children ages 6 to < 12 years old for temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold:

- runny nose
- itching of the nose and throat
- sneezing
- sinus pressure
- minor aches and pains
- itchy, watery eyes
- nasal congestion
- headache
- fever

The proposed dosing regimen for the target population is 10 ml of suspension every 6 hours not to exceed 4 doses a day.

There are multiple OTC cough-cold, decongestant, and allergy single as well as combination drug products available for U.S. consumers. Ibuprofen, pseudoephedrine, and chlorpheniramine have been marketed throughout the world as single-ingredient products.

Ibuprofen is a propionic acid derivative of the non-steroidal anti-inflammatory class of drugs (NSAIDs). It is currently available in four different formulations for the pediatric population: oral drops, suspension, chewable tablets and tablets, all of which have been approved for over-the-counter (OTC) use for temporary relief of minor aches and pains and reduction of fever in children. Ibuprofen is also available in a combination with

pseudoephedrine for children. The dosing of ibuprofen for the single ingredient products and for the ibuprofen/pseudoephedrine combination product differs.

1. Dosing for ibuprofen as a single ingredient for 6 to 11 year old children is a three-tier regimen:
- 6-8 years (48-59 lbs) 200 mg,
- 9-10 years (60-71 lbs) 250 mg, and
- 11 years (72-95 lbs) 300 mg.

   Doses may be repeated as needed every 6 to 8 hours, not to exceed 4 doses in 24 hours.
2. Dosing of ibuprofen in combination with pseudoephedrine for ages 6 to 11 years (weight range 48 to 95 lbs), is 200 mg every 6 hours, not to exceed 4 doses a day. The reason for the approval of the single instead of a three-tier dosing schedule was that the three-tier schedule would exceed the maximum single and daily dose of pseudoephedrine in some of the age categories.

Pseudoephedrine and chlorpheniramine dosing regimens for the triple combination product are consistent with the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC Use Final Monograph. Under the monograph, a dose of pseudoephedrine for children 6 to under 12 years of age is 30 mg every 4 to 6 hours not to exceed 120 mg in 24 hours, and the chlorpheniramine dose for children 6 to under 12 years of age, is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours.

The proposed dosing regimen for the new combination will provide a single dose of ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg. The proposed dosing directions allow repeated dosing every 6 hours, up to 4 doses a day. From the regulatory point of view, the dosing schedule for the new product is appropriate for the proposed age category.

The sponsor's triple combination (IBU 200mg/PSE 30mg/CHLOR 2mg) in a tablet form for adult use (NDA 21-441) was approved on December 19, 2002, under the name Advil Allergy Sinus. However, the triple combination of all three ingredients has not been previously formulated in a suspension for children, either domestically or outside the U.S.

There were several meetings between the sponsor and the Agency during the development phase of the ibuprofen/pseudoephedrine/chlorpheniramine pediatric formulation. The pre-IND meeting for this product was held on March 6, 2001 where the following key issues were communicated to the sponsor:

- The sponsor was requested to provide rationale, as to why a triple combination product is needed to treat allergy symptoms in children, especially given the proposed maximum duration of use of 3 days.
- The Agency raised a concern about possible differences in efficacy in adult and pediatric populations and the potential need for efficacy trials in children.
- Recommendations were also given on the design of pharmacokinetic and clinical safety studies.

The pre-NDA meeting was held on January 8, 2003. The following issues were discussed during this meeting:

- The Agency had a concern about the ——— of the product, and requested the sponsor to design their product's label so that the principle display panel would adequately convey the internal analgesic contained in this triple combination product.
- FDA requested additional data to support the proposed two-teaspoon dose for children (IBU 200 mg/PSE 30 mg/CHLOR 2 mg) in light of the one-caplet dose (IBU 200 mg/PSE 30 mg/CHLOR 2 mg) approved for adults (NDA 21-441).
- Agreement was reached with the sponsor on the content, sources, and timing of updates for their safety database.

This is a safety review of the use of ibuprofen/pseudoephedrine/chlorpheniramine as single ingredients as well as in combination for children 6 to < 12 years of age. There were no efficacy studies submitted as part of this application.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry manufacturing and control is being reviewed by the reviewers in the Office of Pharmaceutical Science.

There is no new preclinical information contained in this New Drug Application.

III. Human Pharmacokinetics and Pharmacodynamics

Two pharmacokinetic studies were conducted: a bioequivalence and food-effects study in healthy adults (AR-00-02) and a bioavailability study in children 6 to < 12 years of age with symptoms of allergic rhinitis (AR-00-03). A brief overview of the design and results of the two studies is included in this section of the review. Safety data gathered during these studies will be discussed in the section of integrated review of safety. In addition, the biopharmacology reviewers will provide in depth review of these studies.

Study AR-00-02:

This was a three-way crossover, randomized, open-label, single-dose, inpatient, single-center trial in healthy adult subjects.

The objectives were:

1) to compare the rate and extent of absorption of IBU, PSE and CHLOR when the suspension was administered under fed and fasted conditions, and

2) to compare the rate and extent of absorption of IBU, PSE and CHLOR when the IBU/PSE/CHLOR combination was administered as a caplet and suspension formulation under fasted conditions, in order to detect any potential formulation effects on the pharmacokinetics of the combination.

There were 15 males (55.6%) and 12 females (44.4%). The racial distribution was 70.4% Black, 25.9% Caucasian, and 3.7% Hispanic. The mean age of all subjects was 28.3 years (range 20-40 years).

Twenty-seven (27) healthy adult male and female subjects received, in a randomized manner, a total dose of IBU 400 mg, PSE 60 mg and CHLOR 4 mg in combination, as follows:

- Treatment A consisted of 20 mL of the IBU/PSE/CHLOR suspension under fasted conditions;
- Treatment B consisted of 20 mL of the IBU/PSE/CHLOR suspension under fed conditions; and
- Treatment C consisted of two caplets of the IBU/PSE/CHLOR combination under fasted conditions.

There was a washout interval of at least seven days and no more than 14 days between each of the three 72-hour study periods. The sponsor stated that pharmacokinetic data derived from 26 subjects showed the following:

- When evaluating the effects of food on the combination suspension, a high-fat meal had no effect (bioequivalence criteria were met) on the area under the curve (AUC) and the maximal observed plasma concentration (Cmax) of PSE (90% confidence intervals (CIs) of 91.12-100.35 and 94.27-100.64, respectively) and CHLOR (90% CIs of 94.22-106.92 and 88.97-98.69, respectively). Food also did not affect the AUC of IBU (90% CI = 85.16-96.96). In contrast, food lowered the Cmax of IBU by 43%, resulting in a 90% CI for Cmax below 80%. This finding is well known for IBU. For at least six hours after dosing, IBU plasma levels were maintained above the minimum effective concentration (6 mcg/mL) for pain relief.
- The suspension and caplet formulations were bioequivalent with respect to PSE (AUCL, 90% CI = 92.94-102.35; Cmax, 90% CI = 90.99-97.14) and CHLOR (AUCL, 90% CI = 92.03-104.43; Cmax, 90% CI = 94.49-104.82). Bioequivalence for IBU AUC was also met (90% CI = 87.94-100.13). Under fasted conditions, IBU in suspension reached a 30% higher Cmax and an earlier Tmax (0.78 and 1.88 hours for the suspension and caplet, respectively), not meeting the Cmax criteria for bioequivalence (90% CI above 125%). The higher IBU Cmax (41 mcg/mL) obtained with the suspension is within therapeutic levels.
- One subject was lost to follow-up and was, therefore, discontinued from the study.

Study AR-00-03:
This was a one-period, one-treatment, open-label, single-dose pediatric pharmacokinetic trial.

The objectives of the study were:

- To determine the total exposure (given by the area under the plasma concentration versus time curve) and the peak exposure (given by the maximum observed plasma concentration of IBU, PSE, and CHLOR) from a single 10-mL dose of Children's Advil Allergy Sinus Suspension in children 6 to < 12 years of age with symptoms of allergic rhinitis;

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

Approximately 32 subjects were to be enrolled in order to ensure that at least 28 completed the study. Enrollment was monitored to obtain an even distribution of age and gender across the participating subjects, with approximately 50% of the subjects between the ages of six and nine years.

Each enrolled subject received a single 10-mL oral dose of Children's Advil Allergy Sinus Suspension, containing IBU 100 mg, PSE 15 mg, CHLOR 1 mg/5 mL under fasting conditions. followed by 20 mL of water. Snacks and meals were provided starting 2 hours after dosing, following the 2-hour blood draw. Blood samples were collected pre-dose (up to 4 hours prior to dosing) and at 0.5, 1, 1.5, 2, 3, 6, 9, 12, 24, and 48 hours post-dose for the analysis of IBU, PSE, and CHLOR. Plasma samples for IBU were analyzed by high performance liquid chromatography (HPLC) up to 12 hours post-dose; plasma samples for PSE and CHLOR were analyzed by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) up to 24 and 48 hours post-dose, respectively.

All AEs that occurred during the study, as well as those that were voluntarily reported by the subject or subject's parent/guardian within 15 days after the completion or withdrawal from the study were recorded. Concomitant medication use was monitored and recorded throughout the study.

Selection of Treatments
Each enrolled subject received a single oral dose of Children's Advil Allergy Sinus Suspension, which translates to a total dose of IBU 200 mg, PSE 30 mg, and CHLOR 2 mg.

Inclusion Criteria
Subjects were eligible for inclusion in the study if they met all of the following criteria:
- Subject was a male or female between the ages of 6 and < 12 years with symptoms consistent with allergic rhinitis, which may have included one or more of the following: runny nose, sneezing, itching of the nose and/or throat itchy/watery eyes, nasal congestion, allergy associated headache, facial pain/pressure/discomfort;
- Subject was in normal physical health (except for symptoms of allergic rhinitis) as judged by the Investigator based on physical examination and laboratory evaluations;
- Subject was within the 5^{th} and 95^{th} percentiles in height and weight for his/her age;
- Parents or legal guardians provided written informed consent and subjects provided their assent, if age-appropriate.

Exclusion Criteria
Subjects were excluded from participating in the study if any of the following were noted:
- Subject had eaten within 8 hours prior to dosing with study medication;

- Subject had ingested any dietary item containing methylxanthines (*e.g.*, cola drinks or chocolate) within 8 hours prior to dosing;
- Subject had a known hypersensitivity to IBU, aspirin or any other nonsteroidal anti-inflammatory drug, PSE or any other sympathomimetic agent, or CHLOR or any other antihistamine;
- Subject had a systolic and/or diastolic blood pressure reading at or above the 90th percentile based on gender, age and height, as presented in the protocol. A subject with no history of hypertension, who had a blood pressure reading at or above the 90th percentile, was allowed to rest for 15 minutes and the blood pressure measurement repeated. Up to three consecutive measurements were allowed. The subject was excluded from the study if he/she continued to have systolic and/or diastolic blood pressure readings at or above the 90th percentile;
- Subject had a history or presence of a hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, hematological, or metabolic disorder;
- Subject had asthma symptoms at the time of study entry or required daily systemic or inhaled asthma treatment;
- Subject had a history or presence of a condition or required the concomitant use of a medication felt by the Investigator to place the subject at increased risk;
- Subject had a clinically significant abnormal laboratory result, as judged by the Investigator;
- Subject was a female who had experienced menarche and had a positive urine-based pregnancy test, or refused to use a medically-accepted form of birth control, including abstinence;
- Subject used a monoamine oxidase inhibitor (MAOI) within two weeks prior to study drug administration;
- Subject used any of the following medications/products within the specified time periods prior to dosing with study medication: CHLOR-containing products within 72 hours, PSE-containing products within 24 hours, any other medications (prescription or over-the-counter), nutritional supplements or herbal products within 12 hours, except acetaminophen which was allowed up to 6 hours prior to receiving study medication;
- Subject was unable or unwilling (as judged by the Investigator) to comply with the requirements of the protocol;
- Subject used an investigational drug or participated in a clinical trial within 30 days prior to entering the study;
- Subject had previously participated in the trial;
- Subject was a relative of the Sponsor, Investigator or other personnel at the research center directly involved with the study.

Results

Thirty-two subjects were enrolled and 30 completed the study. Subject 404 withdrew voluntarily following the 2-hour blood draw. Blood samples for subject 609 hemolyzed. These two discontinued subjects were excluded from all pharmacokinetic analyses since each had at least two consecutive plasma concentrations missing. All 32 enrolled subjects were included in the safety analyses.

There were 13 males (40.6%) and 19 females (59.4%). The racial distribution was 53.1% Caucasian, 31.3% Black, 12.5% Hispanic, and 3.1% other. The mean age of all subjects was 9 years (range 6-11 years).

The pharmacokinetic data derived from the 30 completers showed the following:

- The AUC and Cmax of IBU and PSE, as well as the Cmax of CHLOR in the combination suspension, were comparable (within 16%) for allergy-symptomatic children and healthy adults. In contrast, the AUC of CHLOR was reduced by 27% in children, secondary to a faster clearance of the drug. CHLOR plasma levels remained within the range of concentrations (2-12 ng/mL) known to be effective in alleviating the symptoms of allergic rhinitis.

Table 1 presents a comparison of the pharmacokinetic data obtained for the IBU/PSE/CHLOR suspension in allergy-symptomatic children 6 to < 12 years of age vs. healthy adults.

Table 1. Pharmacokinetic Comparison of Adult's IBU 400 mg/PSE 60 mg/CHLOR 4 mg Dose with Children's IBU 200 mg/PSE 30 mg/CHLOR 2 mg Dose

PK Parameter	Drug	Adult Dose = 20 ml Suspension*	Children 6 to < 12 years Dose = 10 mL Susp.**	% Difference
AUC	IBU	119.04 mcg/mL	112.73 mcg/mL	5.6
	PSE	1961.79 ng/mL	1699.24 ng/mL	15.7
	CHLOR	151.96 ng/mL	113.90 ng/mL	26.7
Cmax	IBU	40.52 mcg/mL	36.58 mcg/mL	11.7
	PSE	211.38 ng/mL	194.83 ng/mL	9.2
	CHLOR	7.95 ng/mL	7.34 ng/mL	14.4
T ½	IBU	2.39 h	1.83 h	23.4
	PSE	5.54 h	4.16 h	24.9
	CHLOR	21.55 h	13.96 h	35.2
CL	IBU	0.05 L/h/kg	0.06 L/h/kg	20.0
	PSE	0.42 L/h/kg	0.56 L/h/kg	33.3
	CHLOR	0.33 L/h/kg	0.52 L/h/kg	57.6

*20 mL susp = IBU 400 mg, PSE 60 mg, and CHLOR 4 mg. Data from clinical study AR-00-02
**10 mL susp = IBU 200 mg, PSE 30 mg, and CHLOR 2 mg. Data from clinical study AR-00-03

Comments:
Overall, the two pharmacokinetic studies show that ibuprofen in suspension is absorbed faster and achieves higher Cmax compared to a solid formulation. The data also show that ibuprofen has a significant food-drug interaction, which is not an unexpected finding. Pharmacokinetic parameters of ibuprofen and pseudoephedrine were comparable in children and adults. Data from the pediatric study show that chlorpheniramine is metabolized faster in children, but its concentration remains within the range known to be effective for relief of allergy symptoms. These conclusions were confirmed with the biopharmacology reviewer.

IV. Description of Clinical Data and Sources

In support of this application, the sponsor submitted the following information:

1. Results of the two bioavailability studies (AR-00-02 and AR-00-03) and study AR-00-04: Children's Advil Allergy Sinus Suspension Multiple Dose Safety Study in Children 6 to < 12 Years of Age With Symptoms Consistent With Allergic Rhinitis, and
2. Safety data from the following sources:
   - Postmarketing surveillance data from WCH and FDA AERS databases,
   - Worldwide literature,
   - American Association of Poison Control Centers,
   - Drug Abuse Warning Network, and
   - Emergency Department Reports.

V. Clinical Review Methods

This review will cover the safety data and proposed labeling. The Division of Anti-Inflammatory and Analgesic Drug Products (HFD-550) will address the chemistry, toxicology, and biopharmacology issues.

The Division of Scientific Investigations (DSI) was requested to inspect one clinical site for each of the three clinical studies: AR-00-02, AR-00-03, and AR-00-04. The report from DSI on the inspection is pending.

The financial disclosure form signed by the sponsor certified that no financial arrangements with the listed 96 clinical investigators had been made where the value of compensation could be affected by the outcome of the study, and that these investigators had no monetary, significant equity interest or any significant payments of other sorts as defined in 21 CFR 54.2.

VI. Integrated Review of Efficacy

The sponsor states that since efficacy was evaluated in an adult population under NDA 21-441, an abbreviated clinical development program was conducted for the ibuprofen/pseudoephedrine/chlorpheniramine suspension drug product.

The efficacy trials for NDA 21-441 used four dosing regimens:
1. Ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg
2. Ibuprofen 400 mg/pseudoephedrine 60 mg/chlorpheniramine 4 mg
3. Pseudoephedrine 30 mg/chlorpheniramine 2 mg
4. Placebo

Both triple combination dosing regimens were statistically superior to placebo for relief of allergy symptoms. There was no added efficacy with a higher dose of the product, and there was a dose-related increase in adverse events. Therefore, the lower dose of the product (ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg) was approved for the treatment of cold and allergy symptoms in adults (one tablet every 6 hours). The sponsor is now proposing the IBU 200mg/PSE 30mg/CHLOR 2 mg dose, only in a different formulation, for 6 to < 12 years old children.

Comments:
The reason for approving a lower dose of the combination product for adults was because of the higher incidence of somnolence with a higher dose of the product. Somnolence is considered to be an adverse effect caused by chlorpheniramine. As shown by the pharmacokinetic data, bioavailability of chlorpheniramine in children is lower, and it's clearance is faster compared to adults. Thus, somnolence from chlorpheniramine 2 mg may not be as big a problem in children.

VII. Integrated Review of Safety

The following sources of safety data were submitted by the sponsor:

1. Safety Data from the 3 Clinical Studies:
    a. AR-00-04
    b. AR-00-02
    c. AR-00-03
2. Postmarketing Surveillance Data from:
    a. WCH database
    b. FDA AERS database
3. Literature review (1/1/2000 - 10/15/2001)
4. Drug Abuse and Overdose Data from the following sources:
    a. American Association of Poison Control Centers (1995-2001)
    b. Drug Abuse Warning Network (1994-2000)
    c. Emergency Department Reports (1994-2001)
5. Four Month Safety Update

Study AR-00-04:

Title
Children's Allergy Sinus Suspension Multiple-Dose Safety Study in Children 6 to < 12 Years of Age with Symptoms Consistent with Allergic Rhinitis

Objective
The objective of this study was to characterize the adverse event profile of multiple doses of Children's Advil Allergy Sinus Suspension, each 10-mL dose containing IBU 200 mg, PSE 30 mg, and CHLOR 2 mg.

Hypothesis
The hypothesis tested was that a 10-mL dose of Children's Advil Allergy Sinus Suspension, administered approximately every six hours, for a total of three daily doses for seven consecutive days, can be safely used to treat symptoms of allergic rhinitis in children 6 to < 12 years of age.

Clinical Sites
This study was conducted at five research centers.

Study Design

This was a multicenter, single-treatment, open-label, non-randomized, multiple-dose safety study of
Children's Advil Allergy Sinus Suspension in allergy-symptomatic children 6 to < 12 years of age. Approximately 120 subjects were targeted for enrollment to ensure that at least 100 completed the study. Table 2 below lists the schedule of events of the study.

Table 2. Study Flow Chart

Assessment	Screening Visit/Day 1	Days 2-7		Final Visit
		Phone Contact #1 (Day 3)	Phone Contact #2 (Day 6)	
Reading of proposed Drug Labeling	X			
Informed Consent and Assent	X			
Medical History	X			
Prior and Concomitant Medication Use	X			X
Physical Exam	X			X
Vital Signs Measurement (temperature, seated blood pressure, heart rate, and respiratory rate)	X			X
Pregnancy Test (if applicable)	X			
Study Drug Administration	X	X	X	
Diary Distribution	X			
Diary Completion	X	X	X	X
Phone Contact		X	X	
Diary Review and Drug Accountability				X
Adverse Experience Monitoring	X	X	X	X

As part of the screening process, the Investigator/designee explained the study requirements to the parent/legal guardian of the prospective study participant. The parent/guardian was presented with and read a copy of the proposed label for Children's Advil Allergy Sinus Suspension, to determine if the use of the combination suspension was appropriate for the child, based on the product's label. Written informed consent was obtained from the parent/guardian and assent from the child prior to the initiation of any study-related procedures. Following consent/assent, a history of medical conditions, medication use and menarche onset (females only) was collected.

Entrance eligibility of potential subjects was determined by the Investigator following a physical examination, monitoring of vital signs, a urine-based pregnancy test for female subjects who had experienced menarche, and an evaluation of the inclusion/exclusion criteria.

Inclusion Criteria

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

a. Subject was male or female 6 to < 12 years of age;
b. Subject was between the 5th and 95th percentiles in body weight and height, based on gender and age, as provided in the protocol;
c. Subject presented with symptoms consistent with allergic rhinitis, as confirmed by physical examination. These symptoms included at least one of the following:

sneezing, runny nose, itchy nose and/or throat, itchy/watery eyes, nasal congestion, allergy associated headache, facial pain/pressure/discomfort;

d. Subject was in general good health (except for symptoms of allergic rhinitis) as judged by a physician Investigator after completing a physical examination;
e. Parent/legal guardian agreed not to administer to the subject and the subject agreed not to take any products, other than study medication, containing IBU, PSE or CHLOR for the seven-day dosing period;
f. Parent/legal guardian read the product's proposed label, as presented in the protocol and agreed that the subject's participation was appropriate under the product's label;
g. Parent/legal guardian was able to read, comprehend, and sign the informed consent form. Child provided assent to study participation.

Exclusion Criteria

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

a. Subject had a known hypersensitivity to IBU, aspirin or any other nonsteroidal anti-inflammatory drug, PSE or any other sympathomimetic agent, or CHLOR or any other antihistamine;
b. Subject had a history of hypertension or presented with systolic or diastolic blood pressure at or above the 90th percentile based on gender, age and percentile height, as provided in the protocol. Note: A subject with no history of hypertension who had a blood pressure reading at or above the 90th percentile was allowed to rest for 15 minutes and the blood pressure measurement was repeated. Up to three repeat seated measurements (taken five minutes apart) were permitted. If the subject continued to have a systolic or diastolic blood pressure reading at or above the 90th percentile, this subject was excluded from the study;
c. Subject had a significant pulmonary, hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, hematological, or metabolic disorder;
d. Subject presented with asthma symptoms at the time of study entry or required the daily use of systemic or inhaled asthma medication;
e. Subject had a history or presented with a medical condition or required the concomitant use of a medication felt by the Investigator to place the subject at increased risk;
f. Subject was female who had experienced menarche and had a positive urine-based pregnancy test or refused to use a medically-approved form of contraception, including abstinence;
g. Subject used a monoamine oxidase inhibitor (MAOI) within two weeks prior to study drug administration;
h. Subject used an IBU, PSE or CHLOR-containing product within 12 hours prior to study drug administration;
i. Subject was unable or unwilling to comply with the requirements of the protocol, as judged by the Investigator;
j. Subject used an investigational drug or participated in a clinical trial within 30 days prior to entering the study;
k. Subject previously participated in this trial;

l. Subject was related to the Sponsor, Investigator or any other personnel at the research center who was directly involved with the study.

Comments:
The conditions for participation in the study were too stringent considering that this drug is intended for an uncontrolled OTC population. Patients were eligible only if they were within the normal range of weight for their age. It is not clear why only these subjects were allowed to enroll. It is not clear why any patient with asthma taking daily medications, was excluded from the study. The proposed label or current practice does not prohibit the use of the three ingredients by these patients. There was no need to exclude subjects who were taking other medications that did not contain an NSAID, PSE or CHLOR or that were not otherwise specifically contraindicated (i.e., MAO inhibitors).

Subject Discontinuation
Subjects were discontinued from the study at any time under the following circumstances:

a. Subject violated any condition of the entrance criteria after having been entered into the study;
b. Subject took more than two doses of a prohibited medication during the seven-day dosing period;
c. Subject missed more than two consecutive doses of study medication during the seven-day dosing period;
d. Subject developed a concomitant illness (and withdrawal from the study was deemed necessary by the parent/guardian and/or Investigator), serious AE, or a hypersensitivity to the study drug;
e. Subject (or parent/guardian) became uncooperative, did not adhere to the requirements of the study protocol, or refused to complete the study;
f. Subject did not return the diary at the completion of the study;

Details of the reason(s) why a subject was discontinued from the study were recorded in the appropriate section of the Case Report Form (CRF). Additional study medication was provided to each site to allow for subject replacement.

Subject Evaluability
An evaluable subject was one who took at least one dose of study medication and had follow-up safety data. A completed subject was one who took study medication for seven consecutive days, did not miss more than two consecutive doses of study medication, did not take more than two doses of a prohibited medication during the seven-day evaluation period, returned the study diary, and completed the physical examination and monitoring of vital signs on the final visit.

Treatment Compliance
The two bottles of study medication assigned to each subject were contained in a medication kit coded with the corresponding subject number. The subject's parent/guardian kept a daily account of the doses of study medication taken by the

subject. Compliance with the dosing regimen was evaluated at the final visit by a thorough review of the subject's diary and accountability of the returned medication.

Study Conditions

The following conditions were adhered to throughout the conduct of the clinical study:

a. Subjects enrolled were those who met all entry criteria and assented to participating in the study and whose parents/guardians determined participation was appropriate based on the product's proposed label, as presented in the protocol and provided written informed consent to the subjects' participation in the trial.
b. Following the screening evaluations, eligible subjects received the first dose of study medication while at the research center. The parents/guardians were then given detailed instructions for all subsequent doses. Parents/guardians were also instructed on the proper completion of the study diary.
c. Subjects were to refrain from taking other products containing IBU, PSE or CHLOR or MAOIs during the seven-day dosing period.
d. On study days 3 and 6, the Investigator/designee reinforced compliance with the protocol requirements during a telephone contact with the subject's parent/guardian.
e. Within 72 hours following the last dose of study medication, the subject returned to the study site for a final visit. At this time, the end-of-study assessments were completed.

Baseline Evaluations

The following assessments were completed for each subject at the screening visit after the informed consent was signed:

- The Investigator/designee obtained a medical history and information on medication use, particularly, the use of analgesic, decongestant, and antihistamine products within 30 days preceding study entry. History of menarche onset was also obtained for female subjects;
- A study physician performed a complete physical examination;
- Vital signs (*i.e.*, temperature, seated blood pressure, heart rate, and respiration rate) were measured;
- Female subjects who had experienced menarche underwent a urine-based pregnancy test;
- The Investigator/designee reviewed the inclusion/exclusion criteria and determined the subject's eligibility. Qualified subjects were enrolled in the study.

Post-Baseline Evaluations

Once the subject was enrolled in the study, the parent/guardian was provided with two 4-ounce bottles of Children's Advil Allergy Sinus Suspension, two dosing cups, and an IRB-approved copy of the product's proposed label.

Subjects received the first dose of study medication while at the research center; this was considered Day 1 of treatment. Parents/guardians were instructed to continue administering study medication approximately every six hours, three times a day for

seven consecutive days, regardless of the presence of allergy symptoms. Each subject was to receive 19-21 doses of study medication during the seven-day dosing period. The total number of doses of study drug taken by any subject depended on the time the first dose was administered on Day 1, with subjects that enrolled in the morning receiving three doses and subjects that enrolled in the evening receiving only one dose.

For each of the seven dosing days, the parent/guardian was instructed to record in the study diary the date and time of each dose and a response to the question, "Has your child experienced any medical condition, other than allergy symptoms, while taking the study medication?" If "any medical condition" had occurred, the parent/guardian was to describe the event, including start and stop dates and times, intensity (*i.e.*, mild, moderate or severe), treatments required and the use of concomitant medications. Specific instructions on how to record the required information in the diary and the procedures to use when making corrections to the diary were also provided to each parent/guardian. On study days 3 and 6, the Investigator/designee contacted the subject's parent/guardian to reinforce compliance with the protocol. During these phone contacts, the parent/guardian was reminded of the proper dosing regimen and the importance of recording the date and time of each dose, the occurrence of any medical condition, and concomitant medications.

Within 72 hours following the last dose of study medication, the subject returned to the study site. During this visit, the following were performed:

- The subject underwent a complete physical examination and monitoring of vital signs (*i.e.*, temperature, seated blood pressure, heart rate, respiration rate);
- The diary and all study medication bottles (used and unused) were collected. The Investigator/designee reviewed the diary with the parent/guardian to ensure completeness and to clarify ambiguous entries. Any inconsistencies between diary recordings and the unused drug supplies were discussed with the parent/guardian and recorded on the CRF;
- All AEs entered in the study diary were reviewed by the Investigator/designee and recorded on the appropriate pages of the CRF. The Principal Investigator determined the relationship to study drug for each AE, and looked for clinically significant changes in the physical examination. AEs were assessed as stated previously.

Statistical Methods

All computations were performed using SAS version 6.12. Statistical analyses were not performed on the data obtained from this study due to its open-label, single-treatment design.

Safety Analysis

AEs were summarized by body system and COSTART term and further summarized according to severity (worst severity in case of multiple events) and relationship to study medication (worst relationship in case of multiple events). Vital signs readings were also summarized.

There were three categories for grading severity of the adverse experiences:

- Mild: either asymptomatic or easily tolerated
- Moderate: discomfort enough to cause interference with usual activity and may warrant intervention
- Severe: incapacitating with inability to do usual activities

The following definitions were used to assign causality or assess relatedness of an adverse drug experience:

- Definite: direct cause and effect relationship between the suspected drug and the adverse experience has been demonstrated
- Probable: direct cause and effect relationship between the suspected drug and the adverse experience has not been clearly demonstrated, but is likely or very likely
- Possible: direct cause and effect relationship between the suspected drug and the adverse experience is uncertain, but may exist and cannot be ruled out
- Remote: cause and effect relationship between the suspected drug and the adverse experience has not been demonstrated, is not likely at this time, and is in fact most improbable, but not impossible
- Unrelated: adverse experience is judged to be definitely not associated with the suspected drug and is considered to be due to extraneous causes

A serious adverse experience is one that:

- Is fatal
- Is life threatening
- Results in permanent or substantial disability/incapacity
- Results in or prolongs hospitalization
- Is a congenital anomaly/birth defect

Results

The disposition of study subjects by site is summarized in Table 3.

Table 3. AR-00-04 Summary of Subject Enrollment by Site

Subjects	Site 1	Site 2	Site 3	Site 4	Site 5	Total
Screened	26	25	25	27	11	114
Enrolled	25	25	25	25	11	111
Evaluable	25	25	25	25	11	111
Withdrew	1	0	0	0	0	1

Each participating site was allowed to enroll a maximum of 25 subjects. With the exception of site 5, which enrolled 11 subjects, all other sites met their maximum subject enrollment. Across the five study sites, 114 subjects were screened for participation; three subjects failed the screening evaluations and were not allowed to enroll: two subjects had body weights above the 95th percentile for their age and gender and one subject had elevated blood pressure readings. A total of 111 subjects were enrolled and were all included in the safety analysis. One subject (10082) terminated the study early.

This subject did not like the taste of test medication and withdrew consent to study participation after receiving two doses of study medication on Day 1.

Protocol Deviations

There were four categories of protocol deviations: inclusion/exclusion criteria, timing of the final visit, compliance with dosing instructions and final drug accountability. The specific deviations for each category are listed below. None of the deviations compromised the integrity of the study.

Inclusion/Exclusion Criteria Deviations

Eight subjects were enrolled in violation of the protocol entry criteria, as follows:

- Subjects 10051and 10102 had body weights at study entry that were below the 5th percentile for their age and gender.
- Subject 10056 was taller than the 95th percentile, while subject 10095 was below the 5th percentile for their corresponding age and gender.
- Subject 10110 was enrolled while on daily treatment for asthma. Although the five subjects referred to above were inadvertently enrolled in violation of the entry criteria, they received study medication for the seven-day evaluation period and were included in the analysis of safety.
- Subjects 10011,10020 and 10095 had diastolic blood pressure readings (Table 4) during the screening evaluation that were at or slightly above the blood pressure criteria stated in the protocol, and no repeat blood pressure measurement was conducted prior to enrollment. An exception was granted for these three subjects (none of whom had a history of hypertension) by the sponsor and they were allowed to remain in the study. All three subjects had diastolic blood pressure readings below their respective 90th percentiles at the final study visit.

Table 4. Subjects with Diastolic Blood Pressure ≥ 90th Percentile

Subject #	Screening Diastolic BP (mmHg)	Final Diastolic BP (mmHg)	95th Percentile Diastolic BP (mmHg)
10011	80	78	78
10020	76	68	76
10095	80	74	75

Timing of Final Visit Deviations

Subjects 10028, 10053, 10073, 10074 and 10100 returned for their final visit four days after taking their last dose of study drug; subjects 10052 and 10082 returned for their final visit five days after taking their last dose of study drug.

Dosing Deviations

- The following subjects took more than the two-teaspoon dose specified in the protocol on at least one occasion: subject 10059 reported taking 2.5-teaspoon doses on two or three occasions; subjects 10103 and 10104 reported filling the dosing cup above the two-teaspoon mark, resulting in taking an extra 40 mL of study drug over the course of the study.

- Subject 10111 took one dose of study medication on Day 8. There were no AEs associated with the extra study medication taken by any of the subjects listed above.
- Table 5 lists those subjects who took less than the corresponding number of doses of study medication. No subject missed more than five doses of study medication.

Table 5. Subjects Who Missed at Least One Dose of Study Medication

No. of Doses Missed	Subject Number
1	10001, 10004, 10030, 10036, 10041, 10052, 10054, 10059, 10063, 10067, 10068, 10071, 10073, 10074, 10075, 10079, 10089, 10107, 10108, 10111
2	10023, 10035, 10047, 10088, 10090, 10101, 10105, 10106
3	10057
4	10056
5	10005

Drug Accountability Deviations
Subjects whose drug accountability was within ± 20% were considered protocol compliant, while those who deviated by more than 20% were noncompliant (Table 6).

Table 6. Subjects Whose Drug Accountability Deviated by More than 20%

Subject Number	Doses Taken	Expected per Protocol Volume (mL)	Actual mL Used	Percent (%) Difference
10007	19	190	237	25
10008	19	190	235	24
10009	19	190	230	21
10013	19	190	230	21
10014	19	190	231	22
10082	2	20	30	50

As indicated in Table 6, six subjects had drug accountability deviations greater than 20%. Five of the six subjects were just over the 20% limit (range 21%-25%), while only one subject had a larger deviation (50%). When questioned by the site coordinator, all six subjects reported that no extra doses of study medication were taken and no study medication was spilled. None of the subjects listed in Table 6 had AEs that were associated with these drug accountability deviations.

Comments:
Overall, there was relatively good compliance with the dosing directions. The protocol deviations seem to be minor and most probably did not affect the results of the study.

The sponsor should not have excluded two patients from the participation in the study because they were overweight. The dose studied in the trial is currently approved for the adult population. Therefore, the use of the new combination drug should only be limited by weight below the minimum weight for a 6 year old child. The two subjects with

weights < 5% inadvertently enrolled into the study were 8 and 10 years old. Their weights were 44 and 52 lbs, respectively. Only one child was outside the targeted weight on the proposed OTC label (48 to 95 lbs).

Demographic Data

The demographic data of the participants are summarized in Table 7.

Table 7. Demographic Data

		N=111
Gender	Male	55 (49.5%)
	Female	56 (50.5%)
Race	Caucasian	86 (77.5%)
	Black	14 (12.6%)
	Asian	1 (0.9%)
	Other	10 (9.0%)
Age (years)	Mean	8.8
	STD	1.7
	Median	9.0
	Range	6 – 11
Weight (lbs.)	Mean	73.4
	STD	20.6
	Median	69.0
	Range	44 – 130
Height (in.)	Mean	53.4
	STD	4.4
	Median	53.0
	Range	44 – 63

An approximately equal number of males (49.5%) and females (50.5%) were enrolled in this study. The majority (77.5%) of the subjects were Caucasian, followed by Black (12.6%), "other" (9.0%) and Asian (0.9%). The mean age of the subjects was 8.8 years (range, 6-11 years); the mean weight was 73.4 pounds (range, 44-130 pounds); and the mean height was 53.4 inches (range, 44-63 inches).

Table 8 summarizes the distribution of study participants in terms of age and sex.

Table 8. Age and Gender Distribution

Age	Males (N=55)	Females (N=56)	Total (N=111)
6	8 (14.5%)	4 (7.1%)	12 (10.8%)
7	13 (23.5%)	8 (14.3%)	21 (18.9%)
8	9 (16.4%)	8 (14.3%)	17 (15.3%)
9	6 (10.9%)	9 (16.1%)	15 (13.5%)
10	8 (14.5%)	15 (26.7%)	23 (20.7%)
11	11 (20.0%)	12 (21.4%)	23 (20.7%)

Per protocol, all subjects enrolled were at least six but less than 12 years of age. Table 9 summarizes the distribution of weight of the enrolled study population.

Table 9. Weight Distribution

Weight (pounds)	Number of Subjects (N=111)
< 50	9 (8.2%)
50-59	26 (23.6%)
60-69	22 (20.0%)
70-79	17 (15.5%)
80-89	14 (12.7%)
> 90	23 (20.9%)

Comments:
The enrolled population was balanced in terms of gender and height. There was an underrepresentation of children of younger age. At the pre-IND meeting, the Agency requested that at least 50% of the pediatric patients be evenly distributed over a 6-9 year age range. The youngest age category included only 11% of the total study population, and all of the 12 children in this age group were above the 50th percentile for their weight.

The basis of dosing for most of the drugs in children is weight. The proposed OTC label lists the weight range of 48 to 95 pounds. The smallest children would be at risk, for the selected treatment regimen. The weight distribution of the study population was skewed to the heavier side. The weight of the proposed age category of 6 to 11 years old children, according to growth charts, ranges approximately from 40 to 120 lbs. Only 9 out of the total of the 111 enrolled children were below 50 lbs.

Medical History
The subjects enrolled in this study were deemed by the Investigator to be in good health. There were 53% of subjects reporting past, and 98% current medical conditions. Most subjects reported a past history of respiratory allergies (93%). Other frequently reported medical conditions included: non-respiratory allergies (25%), asthma (15%), eczema (14%), headache (12%), and attention deficit hyperactivity disorder (8%).

Baseline Allergy Symptoms
All subjects suffered from various allergy symptoms, including sneezing, runny nose, itchy nose and/or throat, itchy/watery eyes, nasal congestion, headache, facial pain/pressure/discomfort. The symptoms of allergic rhinitis reported at baseline (just before dosing) were as follows: nasal congestion (86%), sneezing (68%), runny nose and itchy nose/throat (65%, each), itchy/watery eyes (62%), allergy-associated headache (31%), and facial pain/pressure/discomfort (27%).

Prior and Concomitant Medications
Twenty five percent of the subjects took concomitant medications during the study. At the screening evaluation, 14% reported the ongoing use of medication to treat: seasonal or perennial allergies (6%), attention deficit hyperactivity disorder (5%), other psychiatric disorders (3%) and asthma (1%). None of these were excluded medications. At the final

visit 11% of the subjects reported (as documented in the diary) taking medication during the study. These medications were used to treat: asthma (5%), seasonal or perennial allergies (4%), and earache, backache and fever (1%, each). The sponsor states that these concomitant medications were not expected to confound the results of the study.

Screening Vital Signs and Physical Examination
There were no clinically significant vital signs readings at the screening evaluation. Observations during the screening physical examination detected eight subjects with abnormalities, primarily associated with the ears/nose/throat (n = 6). None of these abnormalities were judged by the Investigator to be clinically meaningful and none precluded entry into the study.

Comments:
During this drug's IND development phase, the Agency suggested that the sponsor monitor renal function by testing urinalysis and blood chemistries before and at the end of the study. This would have given important safety information, however, the sponsor chose not to do this.

Safety Results
Table 10 summarizes the extent of the study medication exposure in the evaluable population.

Table 10. Exposure to Study Medication

Total Doses Taken	**Number of Subjects (%) N=111**
2	1 (0.9%)
15	1 (0.9%)
16	1 (0.9%)
17	2 (2.8%)
18	10 (9.0%)
19	31 (27.9%)
20	56 (50.5%)
21	9 (8.1%)
Total # of Subjects Taking 19-21 Doses	**96 (86.5%)**

Most subjects (96, 87%) took the 19-21 doses of study medication required by the protocol. Except for subject 10111 who mistakenly took one dose of study medication on Day 8, and subject 10082 who withdrew from the study after taking only two doses of study drug, all other evaluable subjects took study medication for seven consecutive days, not exceeding three doses per day. No subject took more than 21 doses of study drug.

Overall, there were a total of 66 AEs reported by 39 (35%) subjects. All reported AEs (by frequency) are shown in Table 11.

Table 11. Adverse Events

Adverse Event	Incidence of AEs, N (%) (N=111)
All Adverse Events	66
Overall Incidence of Adverse Events	39 (35.1%)
Somnolence	13 (11.7%)
Asthenia	9 (8.1%)
Headache	6 (5.4%)
Abdominal pain	5 (4.5%)
Rash	4 (3.6%)
Mouth ulceration	3 (2.7%)
Dizziness	2 (1.8%)
Nervousness	2 (1.8%)
Asthma	2 (1.8%)
Dyspnea	2 (1.8%)
Conjunctivitis	2 (1.8%)
Dry mouth	1 (0.9%)
Emotional lability	1 (0.9%)
Hostility	1 (0.9%)
Laryngitis	1 (0.9%)
Pharyngitis	1 (0.9%)
Rhinitis	1 (0.9%)
Back pain	1 (0.9%)
Fever	1 (0.9%)
Neck rigidity	1 (0.9%)
Anorexia	1 (0.9%)
Dyspepsia	1 (0.9%)
Nausea	1 (0.9%)
Dehydration	1 (0.9%)
Voice alteration	1 (0.9%)
Otitis media	1 (0.9%)
Urination impaired	1 (0.9%)

The majority (n = 54, 82%) of AEs were of mild (22) or moderate (32) intensity. Similarly, most (n = 47, 71%) AEs were not related or remotely related to study medication.

The AE with the highest incidence rate was somnolence (n = 13, 12%). All somnolence events were experienced within a day after receiving the first dose of study medication and most resolved within two days after study drug was first taken. Only two subjects reported experiencing somnolence for longer than two days after receiving the first dose of study medication. Subject 10058 experienced somnolence for six days that resolved on the last treatment day. This was classified by the Investigator as unrelated to study drug. Subject 10061 experienced somnolence for seven days, which resolved the day after the last dose of study medication was taken. The Investigator classified this AE as remotely related to the study drug. Other frequently occurring AEs included: asthenia (n = 9, 8%), headache (n = 6, 5%), and abdominal pain (n = 5, 5%). The majority (n = 8, 73%) of the AEs associated with the digestive system were either mild or moderate in intensity.

Twelve AEs were reported as severe by 11 subjects: somnolence (n = 3), asthenia, headache and mouth ulceration (n = 2, each), fever, abdominal pain and rash (n = 1, each). Only three severe AEs were judged by the Investigator to be definitely, probably or possibly related to study drug: somnolence (n = 1) and asthenia (n = 2). For each of the two subjects (10107 and 10108) who experienced asthenia, the parent reported that the subject experienced fatigue starting 30 minutes after receiving a dose of study medication, which persisted for the remainder of that day.

The other nine severe adverse experiences were either remotely related or unrelated to study drug. Most (n = 8, 67%) severe AEs resolved spontaneously without treatment. Three subjects required treatment for their severe AEs: mouth ulceration (n =2), rash and fever (n=1, each).

The AE most frequently associated with the use of study medication (*i.e.*, AE is either definitely, probably or possibly related to study drug) was somnolence (n = 6), followed by asthenia (n = 3) and abdominal pain (n = 2). Other drug-related AEs (excluding remotely related to study drug) included: headache, anorexia, dyspepsia, nausea, dizziness, hostility, voice alteration, and impaired urination (n = 1, each). All AEs were followed until resolution.

There were no deaths or serious AEs in the study, and no one discontinued due to an AE. No evert trends were observed for any vital signs measurements. One subject had a temperature of 99.6^{0}F at the final visit that resolved spontaneously 8 days after the last dose of study medicine. There were no clinically significant findings at the post-treatment physical exam.

Comments:
The AEs noted during study # AR-00-04 are consistent with the safety profile of the three active ingredients of the new combination, and with the AE profile in the clinical trial of the same triple combination drug in adults (Study # AD-99-02). There were no unexpected AEs noted in this trial. The most common adverse event in children, as well as in adults, was somnolence. In the adult trial, the incidence of somnolence with the same dose of the product was 9.1%, and with the double dose 16.4%. The incidence of somnolence in children in this trial was 12%. There are no dose response trials for this combination drug conducted in the targeted pediatric population. Therefore, we do not know, if a lower dose of the combination drug would provide an equivalent efficacy and a lower incidence of adverse events in children, as was observed in the adult trial.

Conclusion:
The results of the study suggest that the product is safe for the 3 dose per day 7-day treatment of allergy symptoms in the proposed pediatric age category.

Study AR-00-02 Safety Data:

Thirteen subjects (48.1%) reported a total of 22 AEs. Since study AR-00-02 utilized a crossover design, it was possible for a subject to have an AE in one phase but not another. Of the 27 subjects in this study, 11.1%, 19.2%, and 26.9% of subjects experienced AEs during the suspension-fasted, suspension-fed, and caplets-fasted treatment arms, respectively. The summary of AEs is presented in Table 12. Ecchymosis occurred in a total of 5 subjects. The incidence of all other AEs was low, with no specific AE occurring in more than 2 subjects in any given treatment phase. Most AEs (86%) were mild and not related (68%) to study medication.

Table 12. Summary of Adverse Event Experience

Adverse Experience by Body System		Suspension-fasted (N=27) N (%)*	Suspension-fed (N=26) N (%)	Caplets-fasted (N=26) N (%)
Body as a whole	Injection site pain	1 (3.7%)	1 (3.8%)	2 (7.7%)
	Headache	1 (3.7%)	0 (0.0%)	1 (3.8%)
	Injection site edema	0 (0.0%)	0 (0.0%)	1 (3.8%)
Digestive System	Nausea	1 (3.7%)	1 (3.8%)	1 (3.8%)
	Abnormal Stools	1 (3.7%)	0 (0.0%)	0 (0.0%)
	Constipation	0 (0.0%)	1 (3.8%)	0 (0.0%)
Hemic & lymphatic system	Ecchymosis	0 (0.0%)	1 (3.8%)	4 (15.4%)
Nervous System	Dizziness	1 (3.7%)	0 (0.0%)	0 (0.0%)
	Somnolence	0 (0.0%)	0 (0.0%)	1 (3.8%)
Respiratory System	Cough increased	0 (0.0%)	1 (3.8%)	0 (0.0%)
	Rhinitis	0 (0.0%)	0 (0.0%)	1 (3.8%)
Skin	Pruritus	0 (0.0%)	0 (0.0%)	1 (3.8%)
Total		3 (11.1%)	5 (19.2%)	7 (26.9%)

* Number of subjects; One subject may have multiple AEs for each body system.

No deaths or serious AEs were reported and no subjects discontinued treatment due to an AE. There were no clinically significant pre-study laboratory findings. Post-study, 40.7% of subjects had hematocrit levels below the normal range secondary to the multiple blood draws; none were considered clinically significant.

Study AR-00-03 Safety Data:

Nine (28.1%) subjects reported a total of 10 AEs. Somnolence and pain each occurred in 2 (6.3%) subjects. The incidence of all other AEs reported was limited to 1 subject each. A summary of all AEs is presented in Table 13 below.

Table 13. Summary of Adverse Events

Body System	Adverse Event	Number of Subjects (N=32)
Body as a whole	Pain	2 (6.3%)
	Chills	1 (3.1%)
Cardiovascular System	Vasodilatation	1 (3.1%)
Digestive System	Abdominal Pain	1 (3.1%)
Hemic & Lymphatic System	Ecchymosis	1 (3.1%)
Nervous System	Somnolence	2 (6.3%)
Respiratory System	Bronchiolitis	1 (3.1%)
Skin & Appendages	Acne	1 (3.1%)
Total		9 (28.1%)

Most AEs (70%) were mild and not related (70%) to study medication.

No deaths or serious AEs were reported in study AR-00-03, and no subjects discontinued treatment due to an AE.

Comments:
The two bioequivalency studies AR-00-002 and AR-00-03 have a limited value for the assessment of safety of the new formulation. The patient populations were small and the extent of exposure to the drug was limited. There were no new serious or unexpected adverse events reported during the course of the two studies. Most AEs were not drug related.

Postmarketing Surveillance Data Review:

In support of this NDA, WCH reviewed its internal AE database as well as the FDA Adverse Event Reporting System database.

For the sponsor database the time period reviewed was limited to September 15, 2001 through September 30, 2002 since for, NDA 21-441, the sponsor reviewed reports for the time period January 1980 to September 15, 2001. The time period for the AERS database review ranged from April 1, 2001 to March 31, 2002, the last quarter available through Freedom of Information (FOI). For NDA 21-441, the sponsor reviewed reports for the time period January 1969 through March 31, 2001.

Cases documenting the use of IBU, PSE, and/or CHLOR were extracted from the two databases by comparing the names of medical products recorded in these databases with a reference list of product trade and generic names derived from the 2002 edition of Martindale: The Complete Drug Reference. A total of 2,681 non-duplicated, trade or generic drug names were used to search both the sponsor's and the AERS databases. Reports in which one or more of the reference drug names appeared as a suspect drug or in which the reference drug name appeared as a concomitant drug were selected for review.

For this analysis an adverse drug experience report was classified as serious when one or more of the following five outcomes were noted:
1) death;
2) life threatening;
3) required inpatient hospitalization or prolongation of an existing hospitalization:
4) resulted in a persistent or significant disability or incapacity; or,
5) resulted in a congenital anomaly or birth defect.

For cases assembled from reports in which the only outcome noted was "Other", the case was classified as non-serious.

A combined total of five non-serious and serious cases were extracted from the AERS and sponsor's own databases; four cases (80%) were associated with at least one serious outcome and one case was classified as nonserious.

Of the four serious cases, two were found in the AERS database where all three ingredients were identified as suspect. One serious case and one non-serious case were found in the sponsor's database where all three ingredients were identified as suspect. The remaining serious case was found in the AERS database but none of the three ingredients, IBU/PSE/CHLOR, were labeled as suspect. Brief descriptions of the four cases are presented below.

WCH Case #HQ8625020NOV2001
An attorney reported a case of hemoragic stroke, hypertension, and seizures in 44 year old female, who was taking multiple medications, including a cough and cold combination product. The adverse event was assessed as non-related to the cough and cold preparation.

FDA Case # 3655293
French health authorities reported a case of severe vesiculopapular rash requiring hospitalization in a 22 year old female. She had taken multiple products for pain and allergic rhinitis, among which were dexchlorpheniramine, ibuprofen, and pseudoephedrine. These three ingredients were labeled as suspect in the case. The patient eventually recovered.

FDA Case # 3730197
This was a death report (in the AERS database and also in the literature) of a 9 month old male child treated with dextromethorphan, ceftriaxone, Motrin, acetaminophen, pseudoephedrine, chlorpheniramine, and PPA for fever, cough and rhinorrhea. A postmortem blood analysis revealed markedly elevated levels of dextromethorphan, pseudoephedrine, and PPA, which were assessed as the cause of death. Details of the case will be discussed in the literature review section below.

FDA Case # 3660573
The death of an 80 year old female was reported by a physician. The patient had a history of pain and pseudoarthrosis. Oxycodone HCl was named as a suspect drug in the case. Among fourteen concomitant medications taken by the patient, were ibuprofen,

pseudoephedrine, and Tylenol Allergy Sinus. The adverse event was assessed as non-related to a cough and cold preparations.

Comment:
No new safety signals related to the use of the ingredients in this NDA were uncovered during this review of the spontaneous postmarketing AE reports.

Literature Review:

The sponsor submitted a total of 22 publications: 20 for the individual ingredients; seven IBU; one PSE; and 12 CHLOR; and two reports for the concomitant use of the ingredients. The literature consisted of 14 clinical trials, one epidemiological study, one analysis of drug poisoning, and six case reports.

A comprehensive search of seven databases was performed utilizing a standardized strategy that specifically included a combination of the safety-related key words. The searches were restricted to reports that included the intended population (children ages 6 to < 12 years of age). Reports of congenital malformation were not included since these are associated with adult use of the drugs.

To avoid presenting redundant information in this update, and where possible, the search parameter "publication year" (*i.e.*, years searched) was limited to those years not covered in the sponsor's prior submissions for IBU and PSE. For IBU and PSE, the search was conducted from January 1, 2000 through October 15, 2002. All relevant CHLOR literature was obtained without restriction on date of publication up to October 15, 2002.

Ibuprofen
The search resulted in seven manuscripts: three controlled clinical trials, one open-label study, one epidemiological study, one analysis of drug poisoning, and one case report.

1. Kermond S, Fink M, Graham K, Carlin JB, Barnett P. A randomized clinical trial: should the child with transient synovitis of the hip be treated with nonsteroidal anti-inflammatory drugs? Ann Emerg Med 2002; 40(3):294-299.

This randomized, double-blind, placebo-controlled trial assessed the efficacy of ibuprofen in shortening the duration of symptoms in patients with synovitis of the hip. A total of 36 children ages 12 months to 12 years old were enrolled in the study. Seventeen children in the treatment group received ibuprofen 10/mg/kg/dose 3 times a day for 5 days. A total of 6 subjects (4 ibuprofen and 2 placebo treated) reported gastrointestinal symptoms including nausea, vomiting, or diarrhea. None of the adverse events were assessed as serious.

Comment: The study did not reveal any new or serious adverse events for ibuprofen.

2. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. Pediatrics 2002; 109(2):E20.

This randomized, double-blind, acetaminophen-controlled clinical trial assessed the risk of asthma morbidity in children treated for fever. A total of 1879 subjects (6 months to 12 years) enrolled in the study were treated for asthma; among these, 632, 636, and 611 had been randomized to receive one dose of acetaminophen (12 mg/kg), ibuprofen (5 mg/kg), and ibuprofen (10 mg/kg), respectively. Rates of hospitalization for asthma did not vary significantly by antipyretic assignment; compared with children who were randomized to acetaminophen, the relative risk for children who were assigned to ibuprofen, the relative risk was 0.63% (95% confidence interval: 0.24-1.6%).

Comment: The study is limited in terms of extent of exposure to the drug, only one dose. The study did not reveal any new safety concerns for ibuprofen. Specific adverse events were not mentioned in the article.

3. Lesko SM, O'Brien KL, Schwartz B, Vezina R, Mitchell AA. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001; 107(5):5-15.

This is a prospective, multicenter, case-control study to determine whether ibuprofen increases the risk of necrotizing soft tissue infections and all invasive Group A streptococcal (GAS) infections in subjects with primary varicella infection. There were 52 cases of invasive GAS infection, and 172 controls with uncomplicated primary varicella were enrolled, all < 19 years old. There were only 5 cases exposed to ibuprofen, and 13 exposed to both, acetaminophen and ibuprofen. The risk of necrotizing soft tissue infection was not associated with the use of ibuprofen. Risk of any invasive GAS infection was increased among children who had received ibuprofen (OR 3.9, CI: 1.3-12).

Comment: The applicability of the study findings is not clear. The extent of exposure to the study drugs was not specified. The study did not specify adverse events.

4. Byington CL, Spencer LY, Johnson TA, Pavia AT, Allen D, Mason EO et al. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations. Clin Infect Dis 2002; 34(4):434-440.

This was an epidemiological study of 540 children < 19 years of age to determine specific risk factors and the incidence of empyema in children with community-acquired pneumonia. Outpatient treatment with ibuprofen was one of the nonmicrobial variables potentially associated with empyema (OR 7.8, 95% CI: 2.2-32.8; P < 0.0001). The use of ibuprofen prior to hospitalization was also associated with empyema (OR 4.0, 95% CI: 2.5-6.5; P < 0.0001).

Comment: The study did not address the safety of ibuprofen in the proposed OTC population. The ibuprofen dose and duration of treatment were not reported in the article. Specific adverse events for ibuprofen were not reported.

5. Conejo Menor JL, Lallana Dupla MT. Intoxicaciones por antitermicos. Anales Espanoles de Pediatria 2002; 56(4):318-323.

This is an abstract of an analysis of drug poisoning caused by oral antipyretics in the Spanish pediatric population. Out of 13,044 cases of drug poisoning, ibuprofen accounted for 198 (1.5%) of poisonings. Sixty-one (30.6%) of the ibuprofen poisonings occurred in subjects ages 4-11 years old. Most (60.6%) of the poisonings with ibuprofen were considered mild.

Comment: Specific adverse events for ibuprofen were not reported. Prevention of unintentional poisoning is already addressed by OTC label warnings. The abstract does not mention whether these poisonings are intentional or not.

6. Berkovitch M, Press J, Bulkowstein M, Even L, Barash J, Brik R et al. Premarketing surveillance of oral ibuprofen solution in febrile children. Clin Drug Invest 2001; 21:821-825.

This is an open label actual use study in pediatric patients to assess the safety profile of ibuprofen oral suspension. A total of 1564 febrile children participated in the study. The patient age ranged from 1 month to 16.5 years. Exposure to ibuprofen ranged from 1 to 22 doses over 1 to 20 days. Adverse reactions were reported among 26 (1.66%) patients; 18 children vomited immediately after the administration of the drug and it was not readministered. Two children had abdominal pain that resolved spontaneously, two patients reported nausea, and two had diarrhea. Eight children reported experiencing a "bitter taste" from the medication.

Comment: There was a low incidence of adverse events from the short term treatment of fever with ibuprofen. No serious adverse events were reported.

7. Billiemaz K, Lavocat MP, Teyssier G, Chavrier Y, Allard D, Varlet F. Varicelle compliquee d'une fasciite necrosante a streptocoque hemolytique du groupe A. Archives de Pediatrie 2002; 9(3):262-265.

This is a case report of necrotizing fasciitis in a 5 year-old girl with chicken pox. Ibuprofen (400 mg/day) was prescribed for fever 6 days after the onset of chicken pox. Forty hours later the patient developed edematous, erythematous, and bullous lesions in the pelvic area with a necrotic lesion above left inguinal fold. Group A hemolytic streptococcus was found in the hemoculture and at the entry to the skin specimens. The patient was treated with fluid replenishment, antibiotics and surgery. Fever resolved on day 20, all but one lesion resolved by day 40, and a skin graft was performed.

Comment: The role of ibuprofen in the cause of the patient's necrotizing fasciitis is not clear. It seems that the primary cause of the condition was a secondary infection due to group A hemolytic streptococcus.

Pseudoephedrine

There was one case report of movement disorder due to overdose of a combination product containing PSE, carboxinamine, and dextromethorphan.

Nairn SJ, Diaz JE. Cold-syrup induced movement disorder. Pediatr Emerg Care 2001; 17(3):191-192.

An 8-year-old boy presented to the emergency room with complaints of abnormal facial movements, restlessness, and hallucinations. The patient was alert and oriented, with dilated pupils, facial dyskinesia (jaw and tongue), decreased bowel sounds, and warm, dry skin. The day prior to the visit, an error in using the wrong formulation (concentrated drops instead of suspension) resulted in patient receiving a total of 500 mg pseudoephedrine, 40 mg carboxinamine, 80 mg dextromethorphan in two doses during a 4-hour period. The adverse event was attributed to overdose of one or all the active ingredients in a cough and cold syrup.

Comment: This adverse event was due to overdose.

Chlorpheniramine

The search resulted in a total of nine controlled clinical trials and three case reports.

1. Munday J, Bloomfield R, Goldman M, Robey H, Kitowska GJ, Gwiezdziski Z et al. Chlorpheniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. Dermatology 2002; 205(1):40-45.

This is a report of a multi-center, double-blind, placebo-controlled study in 155 children to evaluate chlorpheniramine in alleviating symptoms of atopic dermatitis. The subjects were randomized to receive either a chlorpheniramine elixir containing 2 mg/5 ml of chlorpheniramine maleate or a placebo elixir. The dosing regimen was 2.5 ml (1-5 years) or 5.0 ml (6-12 years) before bedtime every evening for the first two weeks of the study. Parents were allowed to give an additional second dose as long as 3 hours had elapsed since the first dose. After 2 weeks, subjects continuing to suffer from sleeplessness were permitted to take double the bedtime dose (5 ml for 1-5 years, and 10 ml for 6-12 years). Of the 151 subjects, 20 (13%) reported a total of 29 adverse events (14 in the chlorpheniramine group and 15 in the placebo group). No serious adverse events were reported during the trial.

Comment: The enrolled population (patient with atopic dermatitis) and the dosing regimen (fixed 2 or 4 mg dose at bedtime for 4 weeks) are not consistent with the proposed new drug labeling (2 mg dose every 6 hours as needed for 7 days). No serious adverse events were reported during the trial.

2. Tinkelman DG, Kemp J, Mitchell DQ, Galant SP. Treatment of seasonal allergic rhinitis in children with cetirizine or chlorpheniramine: a multicenter study. Ped Asthma Allergy Immunol 1996; 10(1):9-17.

The article reports results of a multicenter, randomized, parallel-group study which compared the efficacy and safety of cetirizine (5-10 mg a single dose or 2 divided doses) and chlorpheniramine (2 mg TID) in 6-11 year old children with seasonal allergic rhinitis (SAR). A total of 181 children were enrolled into the study. Study medications were given for 2 weeks. Adverse experiences were reported by 33.6% of patients in the combined cetirizine groups and 38.1% of patients receiving chlorpheniramine. AEs reported in the chlorpheniramine group were somnolence (7.9%), fatigue and headache (6.3% each), abdominal pain (4.8%), and nausea (1.6%). One patient in the chlorpheniramine group withdrew from the study due to a side effect (not specified in the article).

Comment: The study results showed no new safety signals for chlorpheniramine.

3. Simons FE, Reggin JD, Roberts JR, Simons KJ. Benefit/risk ratio of the antihistamines (H1-receptor antagonists) terfenadine and chlorpheniramine in children. J Pediatr 1994; 124(6):979-983.

This is a double-blind, single-dose, placebo-controlled, three-way crossover study in 15 children (7 to 11 years old) with allergic rhinitis to assess risk/benefit ratio of two H1-receptor antagonists. On three different days the children received terfenadine (60 mg), chlorpheniramine (4 mg), or placebo. The adverse CNS effects of the study medications were assessed by means of the P300-event-related potential, a cognitively evoked electroencephalographic response that is an objective measure of sustained attention and cerebral processing speed, and by a Visual Analog Scale which was based on the Stanford Sleepiness Scale. Results of the study showed that terfenadine did not increase the P300 latency significantly compared with baseline, in contrast to chlorpheniramine, which did increase the latency of P300 related potentials and somnolence over baseline.

Comment: There were no new safety signals for chlorpheniramine.

4. Shanon A, Feldman W, Leikin L, Pong AH, Peterson R, Williams V. Comparison of CNS adverse effects between astemizole and chlorpheniramine in children: a randomized, double-blind study. Dev Pharmacol Ther 1993; 20(3-4):239-246.

This is a prospective, randomized, double-blind, cross-over design study to assess CNS side effects of chlorpheniramine and astemizole in children. One hundred and three children ages 8 to 16 years old with symptoms of allergic rhinitis or hay fever were enrolled in the study; 92 (89%) completed it. Children were stratified by age and randomly allocated to treatment with one of the two medication sequences: astemizole 5 or 10 mg, or chlorpheniramine 10 mg/day. Over a period of 13 weeks both groups had 1 week of baseline studies, 3 weeks of one medication, either chlorpheniramine or astemizole, a 6-week wash-out period and then 3 weeks of the other study medication for a second treatment period. Main outcome measures were: attention span (continuous performance test), short-term auditory and visual memory (visual aural digit span test), visual memory for geometric shapes (Benton visual retention test), motor coordination and visual-motor integration (grooved pegboard test), tapping speed and fine motor

coordination (finger tapping test), physical side effects (sleepiness and dizziness), and compliance.

There were no significant drug effects on the visual retention test and the continuous performance test. On the visual aural digit span test, patients treated with astemizole scored higher than at baseline. Two patients on the chlorpheniramine discontinued the study because of drowsiness. The most common adverse events were dizziness and tiredness. There were no clinical or statistical differences in adverse events between the two medications or between each medication and baseline.

Comment: There were no unexpected adverse events for chlorpheniramine reported during the study.

5. Feldman W, Shanon A, Leiken L, Ham-pong A, Peterson R. Central nervous system side effects of antihistamines in schoolchildren. Rhinol Suppl 1992; 13:13-19.

The authors of the article published a literature review of available studies on the effects of antihistamines on the central nervous system (CNS) in children. The authors also briefly describe a double-blind cross-over design study in 92 children of 8-16 years old studying CNS-effects of astemizole and chlorpheniramine. They conclude that there is no difference in subjective symptoms of sedation or other side effects between the treatment groups.

Comment: No new data were presented in the publication. The study described in the article was published as a separate report (Reference #4).

6. McLoughlin J, Nall M, Berla E. The impact of allergy medication on reading comprehension in children. Ann Allergy 1990; 64(1):86.

This is a brief abstract summarizing a double-blind, placebo-controlled, cross-over design trial in 12 school age children (5 boys and 7 girls) with a history of allergic rhinitis. The investigators evaluated the impact of chlorpheniramine (dose is not reported) on reading comprehension. The mean reading comprehension scores of the drug and placebo groups were 59 and 60 respectively. The authors conclude that even though some drowsiness and or inattention may occur, chlorpheniramine has no effect on reading comprehension test scores.

Comment: Specific adverse events were not mentioned in the abstract.

7. Boner AL, Miglioranzi P, Richelli C, Marchesi E, Andreoli A. Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis. Allergy 1989; 44(6):437-441.

This article reports a randomized, double-dummy study in children 4-12 years of age, assessing efficacy and safety of loratadine and dexchlorpheniramine suspension. A total of 40 children were enrolled in the study; 21 received loratadine (0.11-0.24 mg/kg once a

day) and 19 received dexchlorpheniramine (0.1-0.23 mg/kg every 8 hours) for 14 consecutive days. Four out of 19 children in the dexchlorpheniramine group reported somnolence on day 1, and two reported mild epistaxis during the first 3 days of treatment.

Comment: There were no serious adverse events reported for chlorpheniramine during the 14-day course of the study. The epistaxis could be related to the underlying condition or to the drying effects of the drug. The authors did not discuss attribution.

8. Meltzer EO, Ellis EF, Rosen JP, Shapiro GG, Siegel SC, Tinkelman DG. A comparison of loratadine, chlorpheniramine and placebo suspensions in children with seasonal allergic rhinitis. J Allergy Clin Immunol 1988; 81(1): 177.

This is a brief abstract of a multicenter, double-blind, parallel study in 272 children, aged 6 to 12 years with moderate to severe seasonal allergic rhinitis. Patients were randomized to receive either loratadine (5 mg/5 ml) QD, chlorpheniramine (2 mg/5 ml) BID, or placebo for 2 weeks. Dosing of the medication was based on the weight of the child. Patients weighing < 30 kg had 1 teaspoon and > 30 kg had 2 teaspoons of medication. The incidence of sedation in the chlorpheniramine group (3%) was not different from the placebo treatment (3%). The severity of the events was not reported.

Comment: There were no unexpected adverse events reported during the study.

9. Todd G, Hopkins P, Maclay WP. Double-blind trials of clemastine ("Tavegil") in allergic rhinitis. Curr Med Res Opin 1975; 3(3):126-131.

The article reports results of a double-blind, placebo-controlled trial in 42 children with allergic rhinitis, randomized to receive clemastine elixir (0.5-1.0 mg BID) or chlorpheniramine (2-4 mg BID) for 3 weeks. The age range of the enrolled patients was from 2.5 to 12.3 years (mean 6.9 years). Three out of 23 subjects in the chlorpheniramine treatment group reported drowsiness, and one subject reported nausea.

Comment: There were no unexpected adverse events reported during the study.

10. Nishikawa M, Hikosaka M, Yonemoto T, Gondou A, Tabata S, Ogawa Y et al. A case of iatrogenic growth retardation induced by a corticosteroid-containing anti-allergic drug. Horm Metab Res 1995; 27(8):376-378.

This is a case report of a 9-year old boy with reduced growth velocity while taking betamethasone (0.25 mg QD) and chlorpheniramine (2 mg QD) for 4 years for allergic rhinitis.

Comment: The duration of treatment in the reported patient is much longer than the 7 days proposed treatment duration for the sponsor's combination product. In addition, corticosteroids are known to suppress growth in children, which is the most likely cause of a growth retardation in the reported patient.

11. Yokoyama H, Iinuma K, Yanai K, Watanabe T, Sakurai E, Onodera K. Proconvulsant effect of ketotifen, a histamine H1 antagonist, confirmed by the use of d-chlorpheniramine with monitoring electroencephalography. Methods Find Exp Clin Pharmacol 1993; 15(3):183-188.

This is a case report of development of partial seizures caused by d-chlorpheniramine in a 5-year old boy with medication-controlled epilepsy. Subsequent challenge in an experimental environment with d-chlorpheniramine increased epileptic discharges revealed by electroencephalogram. The authors make a recommendation that centrally-acting histamine H1 antagonists should be avoided in epileptic patients of preschool age.

Comment: The proposed OTC labeling directs all patients under a doctor's care for a serious condition to get an advice from a physician before taking an OTC antihistamine preparation.

12. Hamdan-Allen G, Nixon M. Anticholinergic psychosis in children: a case report. Hosp Community Psychiatry 1991; 42(2):191-192.

This is a case report of an anticholinergic psychosis in a 7-year old girl in response to the treatment with phenylpropolamine hydrochloride (PPA) and chlorpheniramine. From the age of four months, the patient had recurrent urinary tract infections, which were treated with antibiotics. At age of three, she developed urinary frequency due to neurogenic bladder and was started on oxybutynin chloride at a 5 mg a day. A week later, the combination drug, containing 75 mg of PPA and 12 mg of chlorpheniramine, was added. After three weeks on these medications, the patient manifested bizarre behavior, sleep disturbance with nightmares, hyperactivity, anorexia, and incoherent speech. The medications were discontinued, and her symptoms resolved within 24 hours. At age six, she was again started on the same two drugs (combination of PPA and CHLOR, and oxybutynin) at comparable doses. She received both medications for six weeks, until neuropsychiatric symptoms (anxiety, agitation, insomnia, nightmares, and visual hallucinations) led to her hospital admission. Both medications were discontinued, and within one to two days the symptoms subsided without major sequelae.

Comment: Both, PPA and chlorpheniramine, have an effect on the central nervous system, therefore, in this case, it is difficult to attribute the adverse event to one ingredient or another.

Chlorpheniramine and Pseudoephedrine

There was one controlled clinical study, which is described below. A case report that discusses an overdose situation, will be discussed later in this review.

Cantekin EI, Mandel EM, Bluestone CD, Rockette HE, Paradise JL, Stool SE et al. Lack of efficacy of a decongestant-antihistamine combination for otitis media with effusion ("secretory" otitis media) in children. Results of a double-blind, randomized trial. N Engl J Med 1983; 308(6):297-301.

The efficacy of a four-week course of an oral decongestant (pseudoephedrine HCl 4 mg/kg/day, and chlorpheniramine 0.35 mg/kg/day) was compared with that of placebo in a double-blind, randomized trial of 553 infants and children (7 month to 12 years old) who had otitis media with effusion. Side effects were collected at two and four week visits. There was a significant difference in adverse events between the placebo and the treatment group. Mild sedation was the most frequent symptom reported at two weeks (12% of PSE/CHLOR vs. 3% of placebo patients). Other adverse events reported in the treatment group at 2- and/or 4-week visit were irritability, restlessness, lack of appetite, nausea and vomiting. The report did not specify the severity of the events.

Comment: There were no unexpected adverse events reported for the pseudoephedrine/ chlorpheniramine combination product.

Renal and GI Effects of Ibuprofen

To address safety concerns raised by the FDA at the pre-NDA teleconference on January 8, 2003 regarding the use of IBU in children, a literature search was conducted to investigate the renal and GI effects of IBU in children. The search was performed without restriction to publication date up to January 21, 2003 and included all children up to the age of 12 years. Search terms included: "ibuprofen" and "kidney failure," "renal failure," "interstitial nephritis," "papillary necrosis," "nephrotoxicity," "gastrointestinal hemorrhage," "peptic ulcer," "stomach ulcer," "duodenal ulcer," "GI bleed," "GI ulcer," "gastrointestinal bleed", or "melena."

The sponsor's worldwide literature search resulted in a total of 24 publications (listed in Appendix I): two that included both renal and GI safety data, 20 with renal data, and two with GI data. Twelve were controlled clinical trials, two were actual use studies and 10 were case reports/series.

Nine of these citations (References 5-12, and 25) assessed the safety of ibuprofen in preterm or full term neonates, not OTC targeted populations. One article (Reference 15) described four cases of renal function test abnormalities in children with cystic fibrosis. All of the reported cases were confounded with the concomitant administration of another nephrotoxic drug, aminoglycoside. References 13, 19, 20, and 21, case reports of pediatric patients who developed renal side effects following intentional or unintentional ibuprofen overdose. All four patients recovered after the discontinuation of the drug with or without supportive care. Five citations (References 14, 16, 17, 18, and 22) described renal side effects in a total of 7 pediatric patients taking ibuprofen within the range of OTC doses. All except one patient developed progressive renal failure. This was a 7.5 year-old girl with underlying hyper Ig-E syndrome, who was treated with a single dose of ibuprofen 5 mg/kg for fever due to severe pulmonary infection. Her history was also complicated with moderate dehydration. Her renal biopsy showed evidence of cortical and tubular necrosis consistent with an ischemic insult.

The remaining five articles report actual use or controlled clinical studies (References 1, 2, 3, 4 and 24). Two actual use studies, the Boston Fever Study (References 2, 3, and 24), and the Children's Analgesic Medicine Project (Reference 1) examined over 75,000 children ranging in age from 1 month to 12 years who received ibuprofen at OTC and

prescription doses. In the Boston Fever Study the median duration of treatment was 3 days. None of the children in either study experienced either GI or renal toxicity, attesting to the safety of IBU used in this population.

In addition to the worldwide literature search, the sponsor analyzed all available postmarketing adverse event data on renal and GI effects of ibuprofen in children aged 6 through 12 years at OTC doses:

1. Renal Effects
The sponsor conducted a review of reports from their own and the AERS databases from May 18, 1984 through March 31, 2002, and recovered 22 possible cases of ibuprofen use associated with renal events in this population. In 20 of the 22 cases, IBU was either associated with the reported renal event or may have played a contributory role. There were nine cases where ibuprofen was administered with products known to be nephrotoxic. There were no deaths reported. The most common outcome was hospitalization. All but one child recovered.

A review of over 15,000 AAPCC reports for IBU use associated with children aged 6 years to less than 12 years was also performed. The period reviewed ranged from 1994 to 2001. No renal events were reported for this age group.

2. GI Effects
There were 15 cases of ibuprofen associated GI bleeding in subjects aged 6 years to less than 12 years, from January 1, 1969 through March 31, 2002 in the sponsor's and the AERS databases combined. Of the fifteen cases, 12 listed IBU as the primary suspect drug and three indicated IBU was a secondary suspect drug. Of the 15 cases, eight were serious. There were no fatalities reported for this age group.

Comments:
Review of the above cited case reports and safety studies failed to reveal any new information regarding the safety profile of ibuprofen when used by 6 to < 12 years old children at OTC doses. The most common serious side effect of ibuprofen, gastrointestinal bleeding is known, and is already addressed by the ibuprofen OTC labeling.

There was one report of progressive renal failure in a patient with dehydration using OTC dosing of ibuprofen. Other reported cases of renal effects associated with the use of ibuprofen led to a complete recovery. The proposed label for the triple combination lists two warnings related to renal effects of ibuprofen: not to use if the child has kidney disease or if the child is taking a diuretic drug. However, the proposed label does not warn consumers about the use of ibuprofen by children in dehydrated state. This warning is on other OTC single and combination pediatric ibuprofen products. To be consistent with other drugs containing ibuprofen, this warning should be added: Ask a doctor before use if the child has not been drinking fluids or lost a lot of fluids due to continued vomiting or diarrhea.

Drug Abuse and Overdose Information:

The sponsor submitted data from the following sources:
1. Drug Abuse Warning Network (DAWN) Emergency Department (ED) Data (1994-2001).
2. DAWN Medical Examiner (ME) Reports (1996-1999).
3. American Association of Poison Control Centers (1995-2001).
4. Search of the worldwide literature as described previously.
5. Postmarketing reports of drug abuse and overdose collected by the FDA.

1. Emergency Department Data

The sponsor states that there is no evidence suggesting the proposed combination of IBU/PSE/CHLOR would have a significant abuse potential. This conclusion is based on an eight year (1994-2001) review of data generated from the DAWN Emergency Department Reports. Table 14 presents estimates of drug abuse-related ED admissions (episodes) either induced by or related to drug abuse. Included in this table are nine categories of either single ingredient products or combinations of products as presented in the DAWN report. The term, "ED Drug mention," refers to a substance that was mentioned in an acute drug abuse episode. Alcohol is reported only for episodes in which at least one other drug is also mentioned.

Three of the nine categories are presented for comparative purposes and include three widely used, single ingredient analgesics: acetaminophen (APAP); aspirin (ASA) and, IBU. Four other categories are representative of combination products (alcohol-in-combination, IBU/PSE, APAP/CHLOR, and APAP/CHLOR/PSE) and of the remaining two categories, one is an antihistamine (CHLOR) while the other is a decongestant (PSE).

Table 14. ED Drug Mentions for 1994 to 2001

	Mention Frequency by Reporting Year							
	1994	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**
Alcohol-in-combination	160,798 (30.99)	166,907 (32.50)	166,172 (32.33)	171,963 (32.64)	184,991 (34.10)	196,222 (35.37)	204,510 (33.99)	218,005 (34.14)
Acetaminophen	37,293 (7.19)	35,371 (6.89)	37,093 (7.22)	34,867 (6.62)	31,424 (5.79)	27,702 (4.99)	32,835 (5.46)	30,888 (4.84)
Aspirin	14,586 (2.81)	12,701 (2.47)	11,811 (2.30)	11,231 (2.13)	11,696 (2.15)	9,365 (1.69)	11,096 (1.84)	6,137 (0.96)
Ibuprofen	19,588 (3.77)	21,754 (4.24)	17,350 (3.38)	17,647 (3.35)	17,567 (3.24)	14,696 (2.65)	18,338 (3.05)	17,123 (2.68)
Chlorpheniramine	365 (0.07)	467 (0.09)	233 (0.05)	234 (0.04)	76 (0.01)	–	63 (0.01)	181 (0.03)
Pseudoephedrine	2,050 (0.39)	1,723 (0.34)	1,279 (0.25)	1,768 (0.33)	1,331 (0.25)	587 (0.11)	938 (0.16)	846 (0.13)
Ibuprofen/Pseudoephedrine	–	13 (0.002)	–	–	–	–	–	–
Acetaminophen/ Pseudoephedrine	20 (0.004)	8 (0.002)	–	42 (0.008)	289 (0.05)	314 (0.06)	1,116 (0.18)	1,991 (0.31)
Acetaminophen/ Chlorpheniramine/ Pseudoephedrine	205 (0.04)	180 (0.03)	67 (0.01)	–	–	–	–	35 (0.005)
Total	**518,880**	**513,519**	**513,933**	**526,818**	**542,432**	**554,767**	**601,563**	**638,484**

Comment:
It seems that between 1994 and 2001 there was no significant increase in ED mentions of ibuprofen, chlorpheniramine, or pseudoephedrine.

2. DAWN Medical Examiner Data

Table 15 displays "raw" and "consistent panel" drug abuse data collected from the DAWN Medical Examiners (MEs) Reports. Consistent panel is a group of MEs that report to the DAWN for at least 10 months in each of the reporting years. The term "Drug Mention" is used to refer to a substance or drug that is mentioned in a drug abuse fatality report submitted to the DAWN. Since the DAWN participation among MEs is voluntary and varies from one year to the next, direct comparisons of raw data values across years are not possible. Information in this report comes from the six most recent DAWN Medical Examiner Reports (1994 to 1999), and reflects only those facilities that reported to DAWN for at least 10 months. The Consistent Panel Data used in the 1999 report includes data from 134 MEs from 39 metropolitan areas.

Table 15 does not highlight data from the year 2000. For year 2000 data, the DAWN Annual Medical Examiner Data has been renamed and reformatted. The new report is called Mortality Data From the Drug Abuse Warning Network, 2000. The report has been reformatted to highlight individual metropolitan areas; aggregate totals are no longer provided. For the geographic areas surveyed, there are no mentions of the three proposed combination ingredients, either alone or in combination with other substances.

Table 15. Drug Mentions by Medical Examiner

Substance	Mention Frequency by Reporting Year					
	1994	1995	1996	1997	1998	1999
	Raw Data					
Alcohol-in-combination						
Acetaminophen (APAP)						
Aspirin						
Chlorpheniramine						
Ibuprofen						
Pseudoephedrine						
Ibuprofen/Pseudoephedrine						
APAP/Chlorpheniramine	NM	NM	NM	NM	NM	NM
APAP/Chlorpheniramine/ Pseudoephedrine	NM	NM	NM	NM	NM	NM
Total						
	Consistent Panel Data (1999 Report)					
Alcohol-in-combination	--					
Acetaminophen (APAP)	--					
Aspirin	--					
Chlorpheniramine	--					
Ibuprofen	--					
Pseudoephedrine	--					
Ibuprofen/Pseudoephedrine	--					
APAP/Chlorpheniramine	--	--	NR	NR	NR	NR
APAP/Chlorpheniramine/ Pseudoephedrine	--	--	NR	NR	NR	NR
Total	--	--				

*NM: no mention; **NR: not reported.

3. American Association of Poison Control Centers Data

In data purchased from the American Association of Poison Control Centers (AAPCC) for the time period January 1, 1995 and December 31, 2001, there were only two reports, both non-serious, that documented an overdose (one unintentional, one intentional) for the proposed combination product.

4. Overdose Cases Reported in the Worldwide Literature

There was one case report in the literature that described a fatal outcome associated with the combination IBU/PSE/CHLOR.

Gunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of Over-the-Counter Cough and Cold Medications. Pedatrics 2001 Sep; 108(3):E52

This is a case report of death of a 9-month-old boy after an unintentional overdose with several over-the-counter cough and cold medications. According to the article, a 9-month-old male infant experienced heart arrest, tachycardia, erythematous tympanic membranes, vomiting, insomnia, nervousness, increased cough, fever, and emotional lability after receiving numerous doses of unspecified OTC medications containing dextromethorphan, PSE, CHLOR, and phenylpropanolamine. The infant also received one ¾ dropper of Motrin (IBU) and an IM dose of ceftriaxone before he expired.

Comments on drug abuse and overdose data:

The case reported by Gunn et al, 2001 (also reported to the AERS database), is a clear overdose of different over-the-counter medications in a toddler.

The above reviewed data do not suggest that the proposed combination product would have a potential for drug abuse. The overdose issues are addressed by warnings in different sections of the proposed OTC label.

Four Month Safety Update:

A safety data update was submitted by the sponsor during the review of the NDA. It includes updates on all the sources used in the original safety database.

Worldwide literature search was conducted from October 15, 2002 through July 1, 2003 using previously described methods. A total of 4 publications were identified for ibuprofen; two articles and two abstracts. No publications were found for pseudoephedrine or chlorpheniramine or any combination of the three ingredients. According to the sponsor, the results of this search found no new information that would alter the safety profile of the proposed combination product. One published study reported ibuprofen use in newborns, which is not an OTC target population[1]. The second publication reported a case of hypothermia after one dose of ibuprofen in a 7-year old girl with pneumonia[2]. The patient recovered with supportive care. Two abstracts reported cases of acute renal failure in children who took ibuprofen for fever[3,4]. In one abstract, all children with renal failure were moderately dehydrated. In the second abstract, 6 renal cases were reported over a 10 year period. In all cases, the children recovered.

Update on the drug abuse and overdose information included revised estimates according to the new format from:

1. DAWN:
   - Emergency Department Data for the time period 1994-2002.
   - Medical Examiner Data for the time period 1994-2001, and
2. AAPCC for the years 2001 and 2002.

Emergency Department Data

Between 1994 and 2001 the DAWN noted there was an approximate 17% decrease in the number of single ingredient APAP-related ED mentions (Table 16). The trend was analyzed through 2001 because the 2002 data only covered January through June. Similarly, there was a significant decrease, 59%, in the number of single ingredient PSE-related ED mentions for this period. There was no statistically significant change in ED mentions associated with IBU between 1994 and 2001 or for the triple ingredient product

---

[1] Supapannachart S et al. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi hospital. J Med Assoc Thai 2002;85 (Suppl 4): S1252-S1258

[2] Desai PR, Sriskandan S. Hypothermia in a child secondary to ibuprofen. Arch Dis Child 2003;88:87-88

[3] Ulinski T et al. Acute renal failure after antipyretic treatment with NSAID in moderately dehydrated children. 2003; P80a.

[4] Vande Walle J et al. Acute renal failure after ibuprofen. 2003; P81

APAP/CHLOR/PSE. The DAWN noted that the upper respiratory combination APAP/CHLOR demonstrated a large increase in mentions from 20 in 1994 to 1,991 mentions in 2001. However, the 1,991 mentions represented only 0.17% of all drug mentions in 2001. The DAWN did not attribute the large increase in mentions for this category as being related to a drug abuse issue.

Table 16. ED Drug Mentions for 1994 to 2002

Drug Category	Mention frequency by reporting year								Jan-Jun 2002*
	1994	1995	1996	1997	1998	1999	2000	2001	
Acetaminophen	37,293	35,371	37,093	34,867	31,424	27,702	32,835	30,888	13,385
Aspirin	14,586	12,701	11,811	11,231	11,696	9,365	11,096	6,137	3,452
Ibuprofen	19,588	21,754	17,350	17,567	17,567	14,696	18,338	17,123	8,272
Pseudoephedrine	2,050	1,723	1,279	1,768	1,331	587	938	846	333
Chlorpheniramine	365	467	233	234	76	...	63	181	32
Ibuprofen / pseudoephedrine	...	13	...	...	...	6	9	7	1
Chlorpheniramine/ acetaminophen	20	8	...	42	289	314	1,116	1,991	836
Acetaminophen/ chlorpheniramine/ pseudoephedrine	205	180	67	...	...	...	...	35	6
Alcohol-in-combination	160,798	166,907	166,172	171,963	184,991	196,222	204,510	218,005	97,527
Total Drug Abuse episodes	518,880	513,519	513,933	526,818	542,432	554,767	601,563	638,484	308,558
Total Drug Mentions	899,600	900,287	906,366	942,382	981,764	1,014,243	1,099,306	1,165,367	564,196
Total ED visits (in 1,000's)	89,697	88,548	91,189	89,720	89,683	91,100	96,163	100,518	50,017

* Estimates for this time period are preliminary.

According to the preliminary data for 2002, the only statistically significant changes noted between 2002 and 2001 were associated with the combination APAP/CHLOR/PSE. Comparison of the first six months of 2002 with the last six months of 2001 revealed an approximate 70% decrease while a comparison between the first six months of 2002 with the first six months of 2001 revealed an approximate 60% decrease. As shown in Table 16, the number of ED mentions associated with the combination product APAP/CHLOR was consistently lower than the mentions for any of the single ingredient products. Also, the number of mentions associated with single ingredient IBU was consistently lower than those associated with APAP.

Medical Examiner Data

In 2000, forty-three metropolitan areas, covering 137 medical examiner jurisdictions, reported fatalities to DAWN. A total of 11,328 drug abuse fatalities were reported to DAWN from a pool of 91.4 million individuals. IBU, PSE and CHLOR were not mentioned in any of the year 2000 top ten lists nor was the combination product APAP/PSE/CHLOR mentioned in any of these lists.

In 2001, forty-two metropolitan areas, covering 128 medical examiner jurisdictions reported fatalities to the DAWN. Based on census data, a total of about 73.5 million individuals were living within the reporting areas. A total of 9,129 drug abuse fatalities

were reported to the DAWN from a pool of 73.5 million individuals. Single ingredient IBU, PSE or CHLOR were not mentioned in any of the year 2001 top ten lists nor was the combination product APAP/PSE/CHLOR mentioned in any of these lists as well.

Comment:
Based on the review of updated DAWN data, there is no evidence to suggest that the proposed combination of IBU/PSE/CHLOR possesses an abuse potential.

American Association of Poison Control Centers Data
As shown in Table 17, AAPCC recorded a total of 1,190,016 pharmaceutical product exposures (46.6% of all substances) during the time period January 1, 2001 to December 31, 2001 and a total of 1,281,336 pharmaceutical product exposures (47.7% of all substances) during the time period January 1, 2002 to December 31, 2002. Relative to pharmaceutical products, the proportion of exposures associated with single ingredient forms of acetaminophen, aspirin, ibuprofen and ibuprofen/pseudoephedrine formulated together, respectively, were 4.7%, 1.4%, 5.1%, 0.2% during 2001 and 4.6%, 1.3%, 5.1%, and 0.2% during 2002.

Table 17. Selected Exposure and Outcome Data for all age groups from AAPCC 2001 and 2002 Annual Reports for Acetaminophen, Aspirin, Ibuprofen and Concomitant Use of Pseudoephedrine with Ibuprofen

			Ingestion Category				Outcome Category			
	No. of Exposures		Intentional		Unintentional		Major		Death	
Substance	2001	2002	2001	2002	2001	2002	2001	2002	2001	2002
Acetaminophen	56,516	58,337	20,002	19,905	35,705	37,643	829	902	120	119
Aspirin	17,075	17,201	9,593	9,277	7,023	7,413	341	332	66	60
Ibuprofen/ pseudoephedrine	1,913	2,636	165	167	1,697	2,408	6	1	0	1
Ibuprofen	60,304	65,726	16,610	17,051	42,510	47,357	228	253	20	12
Total pharmaceuticals	1,190,016	1,281,336	354,473	376,847	778,311	839,757	22,931	25,373	1,730	2,130
Total non-pharmaceuticals	1,365,471	1,407,184	65,213	69,604	1,268,293	1,304,548	4,536	4,678	316	369
Total substances	2,555,487	2,688,520	419,686	446,451	2,046,604	2,144,305	27,467	30,051	2,046	2,499

For this update, the sponsor also reviewed reports received by AAPCC that documented the ingestion of single ingredient IBU as well as reports documenting the ingestion of the combination product IBU/PSE. Since IBU, PSE and CHLOR were not marketed as a combination product at the time of the reporting period, the sponsor has reviewed reports where IBU/PSE product formulations were co-ingested with single ingredient CHLOR products. For the 6-year-old to 12-year-old age group, AAPCC received only one report in 2001 and only one report in 2002 for this specific combination.

1. Ibuprofen
In the 6- to 12-year-old age category, there were 2,593 reported exposures during 2001 and 2,738 during 2002 for IBU formulated alone without concomitant substances. For the combined years 2001 and 2002, a total of 56 unique events were associated with all cases involving the ingestion of IBU without concomitant substances. As shown in Table 18 (see Appendix II), the number of adverse events reported relative to the number of exposures (average 0.16 events/case) suggests that not every exposure resulted in an adverse event. A total of 22 events (39%) were listed in the reference IBU package insert

hence, these events were classified as labeled. The remaining 34 events were not listed in the package insert and were classified as unlabeled.

There were no fatalities associated with IBU ingestion nor were the reported IBU ingestions associated with a "Major" outcome for the 6-12 year age group.

2. Ibuprofen/Pseudoephedrine

In the 6- to 12-year-old age category, there were 74 reported exposures during 2001 and 133 during 2002 for IBU/PSE formulated together without concomitant substances. For the combined years 2001 and 2002, a total of 16 unique events were associated with the ingestion of IBU/PSE without concomitant substances (see Table 19). A total of 7 events (44%) were listed in the reference IBU and PSE package inserts hence, these events were classified as labeled. The remaining 9 events, were not listed in the package insert and were classified as unlabeled. There were no reports of fatalities nor were there any reports where AAPCC classified the outcome of the exposure as "Major."

Table 19. Reported Events Associated with Ingestion of Ibuprofen and Pseudoephedrine Formulated Together for Children 6 to 12 years

Body System Category	Event	Related Frequency		Not Related Frequency		Unknown if related Frequency		Total		Labeled
AAPCC nomenclature	AAPCC nomenclature	2001	2002	2001	2002	2001	2002	2001	2002	
Cardiovascular	Chest pain	0	0	0	0	0	1	0	1	No
	Tachycardia	0	1	0	1	0	0	0	2	Yes
Dermal	Edema	0	2	1	0	0	0	1	2	Yes
	Hives/welts	0	1	1	0	0	0	1	1	No
	Pruritus	0	2	0	0	0	0	0	2	Yes
	Rash	0	0	0	2	0	1	0	3	Yes
Gastrointestinal	Abdominal pain	1	0	0	1	0	1	1	2	No
	Throat irritation	0	0	1	1	0	0	1	1	No
Neurological	Agitated/ irritable	1	1	0	2	1	1	2	4	No
	Ataxia	0	0	1	1	0	0	1	1	No
	Dizziness/ vertigo	1	1	0	1	0	0	1	2	Yes
	Drowsiness/ lethargy	3	3	0	2	0	0	3	5	Yes
	Headache	0	0	0	1	0	0	0	1	Yes
Miscellaneous	Diaphoresis	0	1	0	0	0	0	0	1	No
	Excess secretions	0	0	0	1	0	0	0	1	No
	Other	1	2	1	2	0	0	2	4	No

3. Ibuprofen/Pseudoephedrine/Chlorpheniramine

During the years 2001 and 2002, for the 6-to 12-year-old age category, there was one report where IBU, PSE and CHLOR were ingested concomitantly. In addition to IBU, PSE, and CHLOR, the 12-year-old female, as a suicide attempt, ingested: APAP (adult formulation), loperamide, ASA (adult formulation), naproxen, multi-vitamin (adult without iron or fluoride), cimetidine and other H2 antagonist, antihistamine / decon /

without opioid / without PPA, APAP / decon / antihistamine / without PPA / dextromethorphan, and other cough/cold preparation (excluding PPA, dextromethorphan). Clinical effects were hypertension and tachycardia, and the patient recovered.

World Wide Review of Adverse Events

1. Sponsor Database

For the time period, October 1, 2002 to April 30, 2003, a total of three reports were received by the sponsor describing the **concomitant ingestion of IBU, PSE, and CHLOR**. All the reports were non-serious in nature. The side effects reported were consistent with the known safety profiles of the three individual ingredients.

For the time period, January 1, 2001 to April 30, 2003, and for the age range of 6- to 12-years, the sponsor received thirty-seven (37) serious case reports where **IBU** was considered a suspect drug. In 15 of these cases (41%) the reporting physician indicated that there was a doubtful relationship between the use of IBU and the reported event(s). A total of 63 events were associated with these cases and a tabulation of these events according to labeling status may be found in Table 20 (see Appendix III). Seventy eight percent (78%) of the reports were from health professionals and 22% of the reports came from non-health professionals. The overall mean age of the subjects in these reports was 7.95 years; no significant differences in gender were noted. Seventy-three percent of the reports originated from non-U.S. sources and the remainder originated from domestic reporters.

Based on the Motrin label used in the original submission, 34 of the events (54%) were labeled while 29 events (46%) were classified as unlabeled. The most common system organ classes associated with the 63 events were Skin and subcutaneous tissue disorders (17 mentions, 27%), Gastrointestinal disorders (11 mentions, 17.5%) and Hepatobiliary disorders (6 mentions, 9.5%).

Three serious cases involving the ingestion of **IBU with PSE** in subjects aged 6- to 12-years old were received by the sponsor during the period, January 1, 2001 to April 30, 2003. All were reported by non-health professionals. Two cases involved the use of an IBU/PSE combination product and a summary for the third case is presented below. For the two cases where a combination product was ingested, (HQWYE504204APR03 and HQ7626225OCT2001) the subjects experienced a more severe manifestation of labeled, allergic-type events. At the time the reports were made to the sponsor the events were resolving.

The third case (HQ8328112NOV2001) involved a 6-year-old boy who received one dose of Dimetapp Cold and Allergy (brompheniramine / PSE) for an unspecified hypersensitivity reaction. Four days later, the child awoke in a lethargic state and complained of a severe headache. A single, 150 mg dose of Motrin was administered. Four hours after the IBU dose the child was reported to have experienced a petit mal

seizure. He was taken to an emergency room where the cause of the seizure could not be determined.

2. FDA AERS Database

Between April 1, 2002 and June 30, 2002, seventeen serious cases describing the concomitant ingestion of **IBU, PSE** and **CHLOR** were reported to FDA. Table 21 displays the demographics and general characteristics of these cases.

Table 21. Demographic Summary and General Report Information associated with IBU/PSE/CHLOR Cases Found in the AERS Database

All Serious Cases: Age in years (n=17)	Mean – 36; Median – 37; Range – 11 to 62
Age in years according to Gender: Female (n=16)	Mean – 36.8; Median – 37; Range – 11 to 62
Age in years according to Gender: Male (n=1)	25 years
Gender	Female – 16; Male – 1
Report Type	Expedited – 17
Report Source	U.S. – 17
Reporter	Health Professional – 5; Non-health Professional – 12
Dechallenge	Positive dechallenge – 0
Serious Outcomes*	Disability – 13; Hospitalization – 8; Required intervention – 5; Life-threatening – 1
* More than one attribute per case is possible	

In addition to the cases that were transmitted by the sponsor to FDA **for single ingredient IBU**-containing products in children aged 6 to 12 years, FDA received an additional 273 cases for this age group where IBU was classified as a suspect drug. The overall mean age of the subjects in these reports was 7.8 years with no significant differences in subject gender noted.

Approximately 10% of these cases (28) were classified as serious. The majority of the reports (57%) originated from health professionals followed by unknown reporter types (25%) and non-health professionals (18%). Fifty-seven percent of the cases originated from domestic reporters and the remaining originated from non-U.S. sources.

Based on age, gender, event date, concomitant medications, and reported events, three of the 28 cases (FDA Case numbers 3746058, 3795937, 3746507) appear to be duplicate reports. Using the same criteria, two other cases appear to be duplicates as well (FDA Case numbers 3550467 and 3703688). Finally three additional cases also appear to be duplicates (FDA Case numbers 3655367, 3702973, and 3697521). Thus of the original 273 cases found, only 23 were judged by the sponsor as being serious. Ten subjects were male and thirteen were female.

The most common serious events reported were Urticaria (5, 21.7%) and Face Edema (4, 17.4%). Edema and Urticaria are both labeled events. A tabulation of all serious events occurring in these cases may be found in Table 22 (see Appendix IV). Of the 23 cases, there was one fatality and a narrative summary is presented below.

(HQ6056217SEP2001) In this report from the French Regulatory Authorities, a 6-year-old male with chicken pox was reported to have ingested Children's Advil Suspension (IBU) for an unknown indication on November 30, 2000. On that same day the child was diagnosed with Reye's syndrome and was hospitalized; he subsequently died and the date of death is unknown. According to the report, the reporting physician doubted a link between Reye's Syndrome and the use of Children's Advil Suspension. Reported concomitant medications included: Amoxicillin; Toplexil (Guaifenesin / oxomemazine / paracetamol / sodium benzoate); and "magamylase" (alpha amylase). The dosage regimen for these drugs is unknown. A duplicate of this report transmitted by another manufacturer was found in the sponsor's search of the AERS database, (FDA Case number 3711094).

In addition to the three serious cases described earlier documenting the **concomitant** ingestion of **IBU** and **PSE** from the sponsor's database, an additional 8 cases were found in the AERS database. No serious outcomes were noted for these reports. The most common reported adverse event was the labeled event, "Vomiting", which occurred in half of the cases.

Comment:
The safety data contained in the four month safety update submission were consistent with the known safety profile of ibuprofen, pseudoephedrine, and chlorpheniramine.

VIII. Dosing, Regimen, and Administration Issues

The label the sponsor proposed for OTC marketing is presented in Appendix V.

The sponsor is proposing a dosing regimen of 2 teaspoons every 6 hours while symptoms persist, not to exceed more than 4 doses a day. The product is not to be taken for nasal congestion for more than 7 days or for pain or fever for more than 3 days.

Comments:
The proposed label dosing directions are consistent with other products containing the three active ingredients. However, the safety of the new combination product in the proposed pediatric population was evaluated when used up to a maximum of 4 doses a day. Therefore, dosing directions should be revised to state: "...take 2 teaspoons every 6 hours while symptoms persist, not to exceed more than 4 doses a day."

IX. Use in Special Populations

The sponsor is requesting the marketing of the triple combination product in children 6 to < 12 years of age. The package label appropriately directs consumers to consult a physician, if the patient is under 6 years of age, or if the weight of the patient is below 48 lbs.

The precautions on the use of drug in special populations, such as patients with underlying medical conditions or those who take concomitant medications, are appropriately conveyed by the label. Those warnings are consistent with other OTC medications containing ibuprofen, pseudoephedrine, and chlorpheniramine.

The proposed label for the new combination product has an adequate GI bleeding warning. A warning about the use of ibuprofen by dehydrated children is on OTC ibuprofen-containing products. The new product's label should carry the same warning: Ask a doctor before use if the child has not been drinking fluids or lost a lot of fluid due to continued vomiting or diarrhea.

X. Conclusions and Recommendations

Ibuprofen has previously been found to be safe and effective for OTC use in children for minor pains and fever. Its long marketing history did not reveal any safety concerns. Renal and gastrointestinal side effects of ibuprofen are addressed by the ibuprofen label warnings.

Pseudoephedrine hydrochloride is also Generally Recognized As Safe and Effective (GRASE) for over-the-counter use individually or as a combination oral nasal decongestant ingredient with dosing up to 120 mg/day for children 6 to < 12 years of age (21 CFR 341.80(d)(1)(ii)).

Chlorpheniramine maleate is GRASE for over-the-counter use as an individual or combination ingredient with dosing up to 12 mg/day for children 6 to < 12 years of age (21 CFR 341.72(d)(3)).

Safety data from the two clinical studies in children of the targeted age, suggest that this triple combination product is safe when used – times daily for for 7 days. One clinical study in adults provided no new safety signals. In addition, the safety profile of the new product is supported by the postmarketing data of these three ingredients, which did not reveal any potential signal or new information regarding their safety profile.

In the opinion of this reviewer, the new ibuprofen 100 mg/pseudoephedrine 15 mg/chlorpheniramine 1 mg suspension is safe for children 6 to less than 12 years of age when the proposed dose is taken – times a day.

The proposed label should be modified in the following ways:

- The principal display panel of the package should clearly identify all three ingredients and a statement of their identity. Listing of the active ingredients should be in a contrasted color from the background, and in a font size that is one half as large as the size of the trade name.
- The label should carry one additional warning: Ask a doctor before use, if the child has not been drinking fluids or lost a lot of fluids due to continued vomiting or diarrhea.

- Dosing directions should be changed from "do not use more than 4 times a day" to "do not use more [redacted]", since this is how the new product was studied.

Daiva Shetty, M.D.
Medical Officer
Division of OTC Drug Products (HFD-560)

Andrea Leonard-Segal, M.D., M.S.
Team Leader
Division of OTC Drug Products (HFD-560)

APPEARS THIS WAY
ON ORIGINAL

Appendix I.

References:

1. Ashraf E, Ford L, Geetha R, Cooper S. Safety profile of ibuprofen suspension in young children. Inflammopharmacology 1999; 7(3):219-225.
2. Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. Pediatrics 1997; 100(6):954-957.
3. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA 1995; 273(12):929-933.
4. Kelley MT, Walson PD, Hayes JR, Edge JH. Safety of Paracetamol and ibuprofen in febrile children. Drug Investigations 1993; 6(1):48-56.
5. Hartmann SE, Langhendries JP, Debauche C, Bernard A, Van Overmeire B. The influence of ibuprofen on renal tubular function in extremely low birth weight infants, a multicenter placebo-controlled evaluation. Ped Res 2002; 51:338A-339A.
6. Lago P, Bettiol T, Salvadori S, Pitassi I, Vianello A, Chiandetti L et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomized controlled trial. Eur J Pediatr 2002; 161(4):202-207.
7. Romagnoli C, De Carolis MP, Papacci P, Polimeni V, Luciano R, Piersigilli F et al. Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates. Clin Pharmacol Ther 2000; 67(6):676-683.
8. Van Overmeire B, Smets K, Lecoutere D, Van de BH, Weyler J, Degroote K et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000; 343(10):674-681.
9. Van Overmeire B, Hartmann S, Harrewijn I, Langhendries JP. Randomized double-blind controlled trial on the renal effects of prophylactic ibuprofen in preterm infants. Pediatric Research 49, 365A. 2001.
10. Pezzati M, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. J Pediatr 1999; 135(6):733-738.
11. Van Overmeire B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed 1997; 76(3):F179-F184.
12. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA 1996; 275(7):539-544.
13. Al Harbi NN, Domrongkitchaiporn S, Lirenman DS. Hypocalcemia and hypomagnesemia after ibuprofen overdose. Ann Pharmacother 1997; 31(4):432-434.
14. Wong W, Coward RJ, Morris MC. Ibuprofen induced acute renal failure in an infant. N Z Med J 2001; 114(1140):431.
15. Kovesi TA, Swartz R, MacDonald N. Transient renal failure due to simultaneous ibuprofen and aminoglycoside therapy in children with cystic fibrosis. N Engl J Med 1998; 338(1):65-66.

16. Moghal NE, Hulton SA, Milford DV. Care in the use of ibuprofen as an antipyretic in children. Clin Nephrol 1998; 49(5):293-295.
17. Schaller S, Kaplan BS. Acute nonoliguric renal failure in children associated with nonsteroidal antiinflammatory agents. Pediatr Emerg Care 1998; 14(6):416-418.
18. Primack WA, Rahman SM, Pullman J. Acute renal failure associated with amoxicillin and ibuprofen in an 11-year-old boy. Pediatr Nephrol 1997; 11(1):125-126.
19. Kim J, Gazarian M, Verjee Z, Johnson D. Acute renal insufficiency in ibuprofen overdose. Pediatr Emerg Care 1995; 11(2):107-108.
20. Wattad A, Feehan T, Shepard FM, Youngberg G. A unique complication of nonsteroidal anti-inflammatory drug use. Pediatrics 1994; 93(4):693.
21. McIntire SC, Rubenstein RC, Gartner JC, Jr., Gilboa N, Ellis D. Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. Pediatrics 1993; 92(3):459-460.
22. Van Biljon G. Reversible renal failure associated with ibuprofen in a child. A case report. S Afr Med J 1989; 76(1):34-35.
23. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. Pediatrics 1999; 104(4):e39.
24. Raju NV, Bharadwaj RA, Thomas R, Konduri GG. Ibuprofen use to reduce the incidence and severity of bronchopulmonary dysplasia: a pilot study. J Perinatol 2000; 20(1):13-16.
25. Desai PR, Sriskandan S. Hypothermia in a child secondary to ibuprofen. Arch dis Child 2003;88:87-88.

Appendix II.

Table 18. All Reported Events Associated with Ingestion of Single Ingredient Ibuprofen for Children 6 to 12 Years

Body System Category	Event	Related Frequency		Not Related Frequency		Unknown if related Frequency		Total		Labeled
AAPCC nomenclature	AAPCC nomenclature	2001	2002	2001	2002	2001	2002	2001	2002	
Cardiovascular	Chest pain	1	0	3	2	2	1	6	3	No
	Tachycardia	1	2	1	2	1	1	3	5	Yes
Dermal	Edema	20	15	4	6	5	4	29	25	Yes
	Erythema/flushed	4	3	2	1	2	1	8	5	Yes
	Hives/welts	9	8	1	1	0	4	10	13	No
	Irritation/pain	2	2	0	0	0	0	2	2	No
	Pallor	0	0	0	1	0	0	0	1	No
	Pruritus	3	5	3	0	2	0	8	5	Yes
	Rash	5	4	7	3	4	5	16	12	Yes
Gastrointestinal	Abdominal pain	39	29	8	10	11	8	58	47	No
	Anorexia	0	0	0	1	0	0	0	1	No
	Blood per rectum	0	0	0	0	1	0	1	0	No
	Diarrhea	3	0	4	3	1	2	8	5	Yes
	Hematemesis	1	1	0	0	0	0	1	1	Yes
	Melena	1	1	0	0	0	0	1	1	Yes
	Nausea	21	34	5	8	11	9	37	51	Yes
	Oropharyngeal edema	1	0	0	0	0	1	1	1	No
	Oral irritation	1	3	0	1	0	0	1	4	No
	Throat irritation	4	2	2	10	1	0	7	12	No
	Vomiting	29	29	19	12	12	13	60	54	Yes
Neurological	Agitated/ irritable	0	2	3	1	1	0	4	3	No
	Ataxia	0	0	0	2	0	0	0	2	No
	Coma	1	0	0	0	0	0	1	0	No
	Confusion	1	1	2	2	0	0	3	3	Yes
	Dizziness/ vertigo	5	2	5	1	0	3	10	6	No
	Drowsiness/ lethargy	21	21	7	5	8	13	36	39	Yes
	Dystonia	0	0	0	1	0	0	0	1	No
	Hallucinations/ delusions	0	0	2	4	1	0	3	4	Yes
	Headache	3	0	12	12	1	3	16	15	Yes
	Numbness	0	0	0	1	0	0	0	1	No
	Peripheral neuropathy	0	0	0	1	0	0	0	1	No
	Seizure	0	0	1	1	0	0	1	1	No
	Slurred speech	0	0	0	1	0	0	0	1	No
	Syncope	1	0	0	0	0	0	1	0	No
	Tinnitus	2	0	0	0	0	0	2	0	Yes
	Tremor	0	0	0	1	1	0	1	1	No

Table 18. Cont.

Ocular	Blurred vision	0	0	1	0	0	0	1	0	Yes
	Corneal abrasion	1	0	0	0	0	0	1	0	No
	Irritation/ pain	3	2	0	0	0	0	3	2	No
	Lacrimation	1	2	0	0	0	0	1	2	No
	Mydriasis	1	0	0	0	1	0	2	0	No
	Red eye/ conjunctivitis	2	2	2	0	0	0	4	2	Yes
	Visual defect	1	0	1	1	0	0	2	1	Yes
Respiratory	Bronchospasm	0	0	1	2	0	0	1	2	Yes
	Cough/choke	1	1	1	1	0	1	2	3	No
	Dyspnea	1	1	0	3	0	2	1	6	Yes
	Hyperventilation / tachypnea	0	0	0	2	0	0	0	2	No
Miscellaneous	Acidosis	1	0	0	0	0	0	1	0	Yes
	ADR to treatment	2	0	0	0	0	1	2	1	No
	Bleeding	0	0	1	1	0	0	1	1	Yes
	Diaphoresis	0	0	0	1	0	0	0	1	No
	Electrolyte abnormality	0	1	0	0	0	0	0	1	No
	Fever/ hyperthermia	2	0	18	32	0	0	20	32	No
	Pain	0	1	2	5	0	0	2	6	No
	Other	5	13	17	18	5	5	27	36	No
	Unspecified	5	5	5	5	5	5	15	15	No

Appendix III.

Table 20. Tabulation of Serious AEs for IBU in the WCH Database for Subjects 6 to 12 Years of Age

Body System Category	Serious Event	# Labeled Events	# Unlabeled Events
Blood and Lymphatic System	Neutropenia	1	0
Eye Disorders	Eye swelling	0	1
	Eyelid edema	0	1
Gastrointestinal System	Abdominal pain	1	0
	Gastric ulcer	2	0
	GI hemorrhage	2	0
	Hematemesis	4	0
	Vomiting	2	0
General Disorders	Edema	3	0
	Pyrexia	0	1
Hepatobiliary Disorders	Hepatitis cholestatic	0	1
	Hepatitis chronic	1	0
	Hepatitis NOS	1	0
	Jaundice cholestatic	0	1
	Jaundice hepatocellular	1	0
	Reye's syndrome	0	1
Immune System	Anaphylactic shock	0	2
	Hypersensitivity	2	0
Infections and Infestations	Cellulitis	0	3
	Erysipelas	0	1
	Hepatic infection	0	1
	Necrotizing fasciitis	0	1
	Sepsis	0	1
	Septic shock	0	1
Injury, Poisoning	Hypothermia	0	1
Metabolism and Nutrition	Dehydration	0	1
Musculoskeletal System	Fasciitis	0	2
Nervous System	Convulsions	1	0
Renal Disorders	Renal failure acute	0	3
Respiratory System	Asthma	0	1
Skin and Subcutaneous Tissue Disorders	Angioneurotic edema	2	0
	Dermatitis medicamentosa	0	1
	Dermatitis NOS	1	0
	Face edema	0	1
	Pruritus	3	0
	Rash	0	1
	Steven Johnson syndrome	3	0
	Swelling face	0	1
	Toxic epidermal necrolysis	1	0
	Urticaria	3	0
Vascular Disorders	Shock	0	1

Appendix IV.

Table 22. Tabulation of Spontaneous Serious Adverse Events in AERS Associated with Single Ingredient Ibuprofen-containing Products Subjects 6 to 11 years.

Body System Category	Serious Event	Total # of Events
Blood and Lymphatic System	Anemia	1
	Lymphadenopathy	1
Cardiac Disorders	Cardiac arrest	2
	Cardio-respiratory arrest	2
	Tachycardia	1
Eye Disorders	Blindness	1
	Corneal disorder	1
	Eyelid edema	1
	Lacrimation increased	1
	Proptosis	1
	Uveitis	2
Gastrointestinal System	Hematemesis	1
	Esophageal hemorrhage	1
	Esophageal perforation	2
	Mouth hemorrhage	1
	Tongue edema	1
	Vomiting	1
General Disorders	Chest pain	1
	Condition aggravated	1
	Drug effect decreased	1
	Fall	2
	Inflammation	1
	Malaise	1
	Necrosis	1
	Edema	2
	Edema peripheral	1
	Pain	3
	Pyrexia	3
	Weakness	1
Hepatobiliary Disorders	Biliary tract disorder	1
	Hepatitis cholestatic	1
	Jaundice cholestatic	1
	Reye's syndrome	1
Immune System	Anaphylactic reaction	1
	Anaphylactic shock	1
Infections and Infestations	Candidal infection	2
	Cellulitis	1
	Erysipelas	1
	Infection	2
	Sepsis	2
	Septicemia candida	1
	Skin and subcutaneous tissue abscess	1
	Staphylococcal infection	1
	Streptococcal infection	1
	Varicella	1

Table 22. Cont.

Injury, Poisoning	Anaphylactoid reaction	1
	Injury	2
	Overdose	1
	Postoperative complications	1
Investigations	Blood alkaline phosphatase increased	1
	Blood glucose increased	1
	Blood potassium decreased	1
	Blood pressure increased	1
	Computerized Tomogram abnormal	1
	Hemoglobin decreased	2
	Laboratory test abnormal	1
	Platelet count decreased	1
	Urinary casts	1
	Weight decreased	1
	Weight increased	1
	White blood cell count increased	1
	Chest X-ray abnormal	1
Metabolism and Nutrition	Anorexia	1
	Dehydration	3
Musculoskeletal System	Fasciitis	1
	Fistula	3
	Neck pain	3
Neoplasms	Renal neoplasm	1
Nervous System	Cerebral hemorrhage	2
	Cerebral ischemia	1
	Coma	1
	Headache	3
	Headache aggravated	1
	Hypoesthesia	3
	Intracranial hemorrhage	1
	Intracranial pressure increased	3
	Loss of consciousness	1
	Tremor	2
Psychiatric disorders	Mental status changes	1
Renal Disorders	Anuria	1
	Glomerulonephritis	2
	Nephritis interstitial	1
	Nephritis	1
	Renal disorder	1
	Renal failure chronic	2
	Renal failure	2
	Renal necrosis	1
	Renal tubular necrosis	2
Respiratory System	Acute respiratory syndrome	3
	Asthma	1
	Dyspnea	2
	Hypoxia	1
	Lung infiltration	2
	Mediastinitis	2

Table 22. Cont.

Skin and Subcutaneous Tissue Disorders	Angioneurotic edema	2
	Dermatitis NOS	2
	Face edema	4
	Pallor	1
	Pruritus	2
	Rash scarlatiniform	1
	Scalp tenderness	1
	Skin desquamation	1
	Skin eruption	1
	Swelling face	1
	Toxic epidermal necrolysis	1
	Urticaria	5
Surgical and Medical Procedures	Hemodialysis	2
	Tracheostomy	1
Vascular Disorders	Aortic aneurysm	1
	Aortic aneurysm rupture	1
	Arterial rupture	1
	Cerebral infarction	1
	Collapse	1
	Hematoma	2
	Hemodynamic instability	1
	Shock	2
	Vascular disorder	1
Total		168

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

/s/

Daiva Shetty
11/14/03 11:12:57 AM
MEDICAL OFFICER

Andrea Segal
11/14/03 11:28:22 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL