CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW

NDA Number:	21-441
Date Submitted:	February 28, 2002
Drug Name:	Ibuprofen/pseudoephedrine/chlorpheniramine (200mg/30mg/2mg)
Trade Name:	Advil® Allergy Sinus Caplets
Sponsor:	Whitehall-Robins Healthcare 5 Giralda Farms, Madison, NJ 07940 Mary Davis (Director, Regulatory Affairs) Tel: 973-660-5825 Fax: 973-660-7181
Drug Category:	NSAID analgesic/nasal decongestant/antihistamine
Indication:	Temporary symptomatic relief for allergic rhinitis
Medical Reviewer:	Christina Fang, M.D.
Secondary Reviewer:	James Witter, M.D., Ph.D.
Review date:	December 6, 2002
Related reviews:	Pulmonary review of study AD-99-02 (C. Lee, 10/25/02) Biopharmaceutical review (T. Ghosh, 8/9/02, 10/7/02) OTC labeling review (M. Benson, 10/4/02; M. Chang, 11/7/02, 12/3/02) DMETS proprietary name review (A. Mahmud, 11/8/02) NDA 21-374 safety review (A. Segal, 4/16/02) Statistical review (S. Choi, 12/16/02) Chemistry review (V. Bhavnagri, 12/12/02)
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THE EXECUTIVE SUMMARY OF THE PRIMARY CLINICAL REVIEW

1. RECOMMENDATIONS

1.1. Recommendations on Approvability

The proposed over-the-counter (OTC) marketing of the combination product ibuprofen 200mg/pseudoephedrine 30mg/chlorpheniramine 2mg is recommended for approval by this reviewer, for the temporary relief of symptoms associated with hay fever, upper respiratory allergies, and common cold.

The major benefit of this combination product is the demonstration of efficacy at one-tablet dose, which was shown to be equally efficacious to that of 2-tablet dose. The recommendation of one-tablet single dose will reduce the dose-related risks associated with the use of the product since doubling of the dose of triple combination from one tablet to 2 tablets was associated with dose-related increase in toxicity as demonstrated in the clinical trial (AD-99-02). The addition of ibuprofen 200mg provides additional therapeutic benefits (refer to discussion in section 6.2.3.1 for detail) with no noticeable increase in the incidence of adverse events (the total events as well as the individual events) based on the multiple-dose clinical study (AD-99-02) results. The triple combination provides a dosing convenience for the target population with allergy-associated pain (headache and/or facial pain). The most frequently observed adverse events (AEs) after 7 days of continuous exposure in the clinical study, were somnolence, dizziness, dry mouth, dyspepsia, insomnia, and asthenia, which were all common AEs known to be associated with the use of the 3 individual ingredients at the therapeutic dose.

A potential risk, which is applicable to all the fixed-dose drug combinations, is the unnecessary intake of an ingredient when it is no longer in need as its target symptom(s) resolve. Another potential risk is the risk for accidental overdose with the concurrent use of multiple OTC cold/flu products (single-ingredient and/or combination products) that contain the same or similar ingredients.

The benefit/risk ratio for the OTC use of this combination product, ibuprofen 200mg/pseudoephedrine 30mg/chlorpheniramine 2mg, is considered acceptable in this clinical reviewer's opinion based on the review of the NDA submission.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of Clinical Program

The drug to be reviewed is a triple combination of ibuprofen 200mg, pseudoephedrine 30mg, and chlorpheniramine 2mg (I/P/C) in an oral caplet dosage form. Each active ingredient belongs to the drug class of analgesics, nasal decongestant, and antihistamine, respectively. The proposed trade name is Advil® Allergy Sinus. There were three clinical studies submitted in the original NDA as shown in the table below:

Table 1. Clinical trial inventory

Study #	*Study type*	*Study design*	*Treatment group*	*# Subjects*
AD-99-03	Drug interaction PK study	Single-dose complete crossover	I/P/C 400/60/4 mg	29
			Ibuprofen 400mg	28
			Pseudoephedrine 60mg	28
			Chlorpheniramine 4mg	28
AD-99-01	Food effect PK study	Single-dose complete crossover	I/P/C 400/60/4 mg fast	12
			I/P/C 400/60/4 mg fed	12
AD-99-02	Efficacy and safety study	Multiple-dose, multiple-center randomized, double blind, placebo-controlled, parallel, dose-response, partial factorial	I/P/C 400/60/4 mg	269
			I/P/C 200/30/2 mg	263
			P/C 30/2 mg	273
			Placebo	265

2.2. Efficacy (Study AD-99-02)

The triple combination at both one-tablet (200mg/30mg/2mg) and 2-tablet (400mg/60mg/4mg) dose levels was demonstrated to be efficacious as measured by statistically significantly better ($p<0.001$) performance than placebo in terms of the primary and all the secondary efficacy parameters. The minimum effective dose was demonstrated to be the one-tablet dose. Also, there were no statistically significant separations between the one-tablet and 2 tablet dose of the triple combination in any of the efficacy parameters studied, suggesting the lack of dose response between the two dose levels. The efficacy findings of no additional benefits from the 2-tablet dose supported the dose recommendation of one tablet.

Ibuprofen was shown to contribute to the analgesic effect of the triple combination on relieving allergy-associated pain. The combination with ibuprofen had

significantly better statistical performance than the combination without ibuprofen as measured by SPID3 after the initial dose and by the parameter defined as the incidence of pre-dose pain measured three times a day over the seven day treatment period.

The component contribution of chlorpheniramine 2mg to the antihistamine effect would be better evaluated by comparing the combinations with and without 2mg of chlorpheniramine. Chlorpheniramine 2mg when being used together with ibuprofen and pseudoephedrine had an effect on relieving antihistamine-related symptoms at a level lower than what had been defined in the OTC monograph. The combinations containing chlorpheniramine 2mg (with and without ibuprofen) were statistically superior to placebo in terms of the overall average of total scores (OATSS) and the overall average of antihistamine scores (OATASS) (refer to table 5 for the definition of parameters).

2.3. Safety

There is a long marketing history for the three individual ingredients: ibuprofen, pseudoephedrine, and chlorpheniramine when they are used as single-ingredient products or as OTC combination products. The safety profiles of these individual ingredients have been well established. Various ibuprofen-containing products of different formulations at both prescription and OTC dose levels had been evaluated in multiple NDAs over the years. Pseudoephedrine, and chlorpheniramine were generally recognized as safe and effective for OTC use with dosing up to 240 mg/day and 24 mg/day, respectively, for adults and children over 12 years, per 21 CFR 341.80(d)(1)(ii) and 341.72(d)(3). Various combination products containing pseudoephedrine, chlorpheniramine, or both active ingredients have also been submitted for NDA review and approved in the past years.

The results of the single-dose PK trial (AD-99-03), in which the triple combination was compared to the single-ingredient products did not suggest drug-drug interactions between the three active ingredients in the combination.

Among the 1111 subjects enrolled in the three clinical studies the exposure to the triple combination included any exposure in 573 subjects in 3 clinical trials, of whom 520 subjects had taken at least 19 doses of the triple combination (study AD-99-02). Slightly more than half of those who took the triple combination for about 7 days was exposed to the two-tablet dose. The 7-day exposure to the one-tablet dose of the double combination (pseudoephedrine and chlorpheniramine) was experienced by 263 subjects and to placebo by 273 subjects.

In the multiple-dose safety study (AD-99-02) the total number of subjects reporting AEs in the one-tablet group (24%) was similar to that of the placebo group (20%). The most frequently reported AEs were somnolence, dizziness, dry mouth, dyspepsia, insomnia, and asthenia, known to be the most common AEs associated with the use at therapeutic doses of the three individual ingredients. Most events were rated as mild to moderate in severity. There were no serious events or deaths. Only a relatively small percentage (≤2%) of subjects (in each study group) had early terminations due to AEs. There were dose-related increases in the total number of subjects reporting AEs and most frequently reported specific AEs and dose-related increase in the number of early terminations due to somnolence, when the dose was increased from one tablet to two tablets. The addition of ibuprofen (only studied at 200mg level) to the double combination was not shown to increase AE incidence. Incidence of AE was too low in the single-dose PK studies (AD-99-01 and AD-99-03) to provide useful information for the treatment comparison. There were no new safety signals for the individual ingredients based on the review of safety information from post-marketing surveillance and literature (refer to discussions in section 7.4). The safety information on the concurrent use of the products containing one or more than one of the three active ingredients was very limited for various possible reasons (refer to section 7.5 and 7.6 for detail). The review of post-marketing surveillance data on serious cases reported with the concurrent use of the 3 active ingredients suggested a need for the OTC review division to study the extent of the concurrent use of multiple OTC cold/flu products containing the same or similar ingredients in the OTC population and the magnitude of its associated risk.

Taking all the following factors into consideration: the safety profiles of the individual ingredients for OTC use, the lack of drug-drug interactions between the active ingredients as suggested by the PK study (AD99-03), the AE reporting frequency and the nature of events as observed in the clinical study (AD-99-02), in which more than 500 subjects were exposed for 7 days, the safety database was considered acceptable in this particular case.

2.4. Dosing, Regimen, and Administration

The dosing recommendation should be based on the benefit/risk ratio. As shown in the multiple-dose study (AD-99-02) the doubling of the dose of the triple combination did not improve efficacy but increase dose-related adverse events known of being associated with the three individual ingredients (somnolence, dizziness, dry mouth, dyspepsia, asthenia, and nausea commonly associated with

chlorpheniramine, insomnia associated with pseudoephedrine, and dyspepsia and nausea associated with ibuprofen). This reviewer agrees with the dosing proposed by the Sponsor: one tablet (ibuprofen 200mg/pseudoephedrine 30mg/chlorpheniramine 2mg) every 4 to 6 hours and not to exceed 6 tablets per 24 hours. The maximum daily dose for each individual ingredient in the combination is within the limit set for the OTC use of the corresponding single-ingredient products (1200mg for ibuprofen, 240mg for pseudoephedrine, and 24mg for chlorpheniramine).

2.5. Drug-Drug Interactions

PK study (AD-99-03) results did not suggest drug-drug interactions between the three active ingredients. Drug-drug interactions between the triple combination (containing ibuprofen, pseudoephedrine, and chlorpheniramine) and the other commonly used medication by the general population could not be adequately assessed in the multiple-dose trial (AD-99-02) because of the wide variation in the use of concomitant medication. Drug-drug interaction information for each of the three individual ingredients (ibuprofen, pseudoephedrine, or chlorpheniramine) has been well documented in various drug information sources (PDR, pharmacology textbooks, etc.) in the past.

2.6. Special Populations

Based on the subgroup analysis of PK data, gender effect was shown in terms of the slightly (borderline) lowered Cmax (the extent of maximum absorption) of ibuprofen in the triple combination in males (AD-99-03). Also, food affected the absorption of pseudoephedrine in the triple combination in males as shown by the slightly (borderline) lowered Cmax and AUC (the total absorption) (AD-99-01). These borderline changes on group mean values were not expected to correlate to clinically significant changes.

Females reported more AEs in general and per treatment group than males (refer to table 8). Males and females had a similar pattern in terms of the doe-related increase in AE reporting.

Subjects younger than 18 years old reported less AEs per treatment arm than the three older age groups (refer to table 8). Elderly would be expected of having higher risks for drug-related AEs especially in terms of somnolence and dizziness. However, the comparison of the AE reporting between the elderly and non-elderly

could not be made since only few elderly subjects were included in the study. More elderly should have been included in the multiple dose trial (AD-99-02) for adequate safety analysis of age effects on elderly. On the other hand the dosing recommendation for the triple combination is one tablet for a single dose, which would help to reduce the risks associated with the use of the drug in the elderly. The subgroup analysis based on race could not be conducted because there was not sufficient number of subjects of ethnic minorities to provide valuable information.

CLINICAL REVIEW

1. BACKGROUND

1.1. Introduction

The sponsor has developed a triple combination product, Advil® Allergy Sinus oral caplets, which contains 3 ingredients: ibuprofen 200mg, pseudoephedrine HCl 30mg, and chlorpheniramine maleate 2mg, of the drug class of analgesics, nasal decongestant, and antihistamine, respectively. The originally proposed indication by the Sponsor is [redacted] The proposed dosage is one caplet every 4-6 hours while symptoms occur and not more than 6 caplets in any 24-hour period in patients 12 years of age and older.

1.2. Important Milestones in Product Development

At the pre-IND meeting with the Sponsor dated May 30, 2000, the Division questioned about the component contributions by ibuprofen and by 2mg chlorpheniramine (one half of the Monograph recommended dose). The Sponsor was recommended to include allergy patients with pain and a partial factorial design (combinations with and without ibuprofen) in the study. The Division also recommended the study of the minimum effective dosing and dose-response, the use of regular dosing instead of PRN (take as needed) dosing, and the study of food effect. At the pre-NDA meeting dated November 29, 2001, the discussion was focused on the NDA presentation format, the statistical analysis plan, and the source of safety database. The statistical reviewer recommended the inclusion of all randomized patients as the ITT (intention-to-treat) population, the subjects taking prohibited medication to be treated as treatment failures, the pre-specified procedures for analysis of missing data, and the use of actual recording time and corresponding scores in calculating the time-weighted sum of pain intensity difference. In terms of the safety database the recommendation was to include worldwide safety surveillance and literature search in addition to the surveillance reports to the Sponsor and FDA, with a focus on the safety information related to the concurrent use of the 3 active ingredients. The Sponsor agreed with most of the recommendations with the reservation of the ITT population being patients who had at least one post-dosing evaluation.

1.3. Other Relevant Information

The ibuprofen/pseudoephedrine/chlorpheniramine combination has not been marketed in any country.

1.4. Important Issues with Pharmacologically Related Agents

The combination of an analgesic, nasal decongestant, and antihistamine is listed in the Tentative Final Monograph for Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Combination Drug Products. There are at least 17 different brand names of the OTC combination products containing 2mg chlorpheniramine, 30mg pseudoephedrine, and 250-500mg acetaminophen and at least 3 more products containing the same ingredients at the higher dosing levels, i.e., 4mg chlorpheniramine, 60mg pseudoephedrine, and 650-1000mg acetaminophen already on the U.S. market. There has not been any market withdrawal of these products due to special concerns of safety or effectiveness.

2. SIGNIFICANT FINDINGS FROM CHEMISTRY

The information on manufacture and control of the drug substance for ibuprofen and pseudoephedrine HCl was considered adequate based on the previous review of the corresponding DMFs. The deficiencies identified in the DMF for chlorpheniramine maleate had been resolved and documented in the Sponsor's response to the Pulmonary Division dated June 20, 2002, per chemistry review (refer to chemistry review for detail).

A unique feature in the process of making the triple combination product was the [redacted] The in-process control of quality for the manufacture of the drug product was considered acceptable. The drug product was tested stable at 25°C, 30°C, and 40°C for 12 months. The manufacturing facilities had been inspected by the Division of Compliance and were rated as acceptable. The sponsor was exempted from environmental assessment because the estimated release to the environment was very low.

Many deficiencies have been identified during the chemistry review process and conveyed to the Sponsor. The responses to the deficiencies from the Sponsor were considered acceptable based on chemistry reviewer's evaluation.

3. HUMAN PHARMACOKINETICS

There were two PK trials of a single-dose and complete crossover design conducted in healthy volunteers. One was a 4-arm drug-drug interaction study, in which the combination was compared to each active ingredient administered alone (AD-99-03). The second study was designed to look at food effect on the absorption of the individual ingredients in the triple combination (AD-99-01).

3.1. Drug-Drug Interaction PK Study (AD-99-03)

Based on PK data Tmax (the rate to reach maximum concentration), Cmax (the maximum concentration), and AUC (the total concentration) of the individual ingredients: ibuprofen, pseudoephedrine and chlorpheniramine in the triple combination were within the range defined by FDA standards as bioequivalent to that of the single-ingredient products.

3.2. Food Effect PK study (AD-99-01)

The presence of food did not change AUC and Cmax of the individual ingredients of the triple combination but resulted in the delay of Tmax by about one hour for pseudoephedrine and chlorpheniramine.

4. DESCRIPTION OF CLINICAL DATA SOURCES

4.1. Efficacy Data

There was only one efficacy study (AD-99-02) in the NDA submission.

4.2. Safety Data

Safety data sources included clinical trial data, literature review (data sources: MEDLINE, EMBASE (Alert), EMBASE, BIOSIS, Derwent Drug File, and SciSearch database, as provided by the Sponsor) and post-marketing spontaneous reports. The clinical trial safety data were mainly the adverse events reported in the controlled efficacy/safety study (AD-99-02) and the two PK studies (AD-99-01 and AD-99-03). The literature review was focused on the chlorpheniramine containing products because the safety of ibuprofen, pseudoephedrine, and their combination was recently reviewed in the NDA 21-374 submitted by the same Sponsor (refer to the medical review dated April 26, 2002). The review of the post-marketing spontaneous reports was focused on the concurrent use of the product containing one or more than one of the 3 active ingredients.

5. CLINICAL REVIEW METHODS

5.1. Efficacy Review of the Study AD-99-02

Dr. Charles Lee from the Division of Pulmonary and Allergy Drug Products has reviewed the efficacy trial in detail upon a request for consultation with regard to the contributing effect of chlorpheniramine 2mg to the relief of allergy symptoms. The efficacy review by this reviewer is focused on the component contribution by ibuprofen. The format of this efficacy review is to summarize the key features of the protocol in a table followed by presentations and discussions of the important information on the following topics: demographic and other baseline characteristics, study execution and drug exposure, and efficacy results. This reviewer has generated all the tables in the review based on the data provided by the Sponsor.

5.2. Data Quality and Integrity

Inspection of the selected study sites by the Division of Scientific Investigation revealed no major deficiencies that would compromise the integrity of data.

5.3. Financial Disclosure

The financial disclosure forms signed by the sponsor certified that no financial arrangements with the listed 49 clinical investigators had been made where outcomes affects compensation and that these investigators had no proprietary, significant equity interest or any significant payments of other sorts as defined in 21 CFR 54.2(f). The financial disclosure information is considered acceptable because of the lack of evidence suggesting any conflict of interest in the conduct of clinical trials.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The triple analgesic/nasal decongestant/antihistamine combination product at both dose levels: ibuprofen/pseudoephedrine/chlorpheniramine 200mg/30mg/2mg (one tablet) and 400mg/60mg/4mg (2 tablets) was shown to be efficacious (statistical superiority than placebo, $p<0.001$) in relieving the symptoms of seasonal allergic rhinitis. The 2-tablet dose of the combination was not shown to be more effective than the 1-tablet dosing (no statistically significant differences in any of the efficacy parameters studied).

6.2. Detailed Review of Efficacy

The study AD-99-02 was conducted between February 13, 2001 and July 11, 2001 and the study report is available as archival paper copy volumes 79 to 81 and at clinstat\allergicrhinitis\ad9902\ad9902.pdf electronically.

6.2.1. Protocol (AD-99-02)

Table 2. Protocol summary

Study objective	Evaluating contribution by ibuprofen in relieving pain symptoms associated with seasonal allergic rhinitis and determining the minimum effective dose for the triple combination as well as for the antihistamine component, chlorpheniramine 2mg in the combination
Study design	Multiple-dose, randomized, double blind, placebo-controlled, parallel, dose-response, and partial factorial study at 49 centers in the U.S.
Study population	Male and female healthy subjects age ≥12 years with at least a two-year history (by self-report) of seasonal allergic rhinitis involving any of the following symptoms: runny nose, itchy/watery/red eyes, nasal congestion, sneezing, itchy nose/throat/palate, allergy-associated pain (i.e., headache, facial pain/pressure/discomfort) and a history of at least moderate pain that worsened during the allergy season and responded to the treatment with OTC analgesics, who displayed a positive skin prick test or intradermal test (defined by wheals of at least 3 mm or 7mm above control, respectively), to a standard pollen/grass/tree/mold extract, where aeroallergens prevalent during the current allergy study season were used (refer to the list of inclusion/exclusion criteria for detail)
Baseline condition	Moderate to severe allergy-associated pain (i.e., headache and/or facial pain/ pressure/discomfort) and an accumulative allergy symptom score of at least 48 of 108 based on 6 assessments over 3 consecutive days prior to dosing

Treatment	One dose of the following treatments every 6 hours for 3 doses per day (morning, midday, evening) up to a total of 19 to 21 doses over 7 days (regardless of the presence of allergy symptoms) 1. Ibuprofen 400mg/pseudoephedrine 60mg/chlorpheniramine 4mg; 2. Ibuprofen 200mg/pseudoephedrine 30mg/chlorpheniramine 2mg; 3. Pseudoephedrine 30mg/chlorpheniramine 2mg; 4. Placebo
Concomitant medication	Not allowed: analgesics, anti-inflammatory drug, corticosteroid, decongestant, antihistamine, mast cell stabilizer, leukotriene inhibitor, other therapy for treating allergy symptoms such as herb, nasal saline, eye washes/drops, sedative/hypnotic, psychotropic medication, or drugs known to alter consciousness and mental status
Raw efficacy data	1. Allergy-associated pain (headache and/or facial pain/pressure/discomfort) at 2 and 3 hours after the initial dose, using a 4-point categorical scale (0=not present, 1= mild, 2=moderate, 3=severe); 2. Allergy-associated pain prior to each subsequent dose using the same scale as described above; 3. Reflective (over last 12 hours) assessment of severity of 6 allergy symptoms: nasal congestion, sneezing, rhinorrhea (runny nose), itchy nose/throat/palate, itchy/watery/red eyes, and allergy-associated pain, twice a day (before and after bedtime), using a 4-point categorical scale (as described above) for each individual symptom; 4. Overall assessment (patients' global) on day 7, using a 5-point categorical scale (0=poor, 1= fair, 2=good, 3=very good, 4=excellent);
Efficacy parameter	Primary efficacy parameter: Change from baseline (CFB) in the Overall Average reflective Total Symptoms Score (OATSS); Key secondary efficacy parameters: 1. The time-weighted sum of the pain intensity difference at 2 and 3 hours after the initial dose (SPID3); 2. CFB in the Overall Average reflective Total Antihistamine Symptom Score (OATASS) (sneezing, itchy/watery/red eyes, itchy nose/throat/palate); Other secondary efficacy parameters are defined in detail in the footnote of table 6
Statistical plan	ITT population: eligible subjects taking at least one dose of a test drug and had a total symptom score for the evening of study day 1 or at least one such score in days 2-7; Model for analysis: ANOVA with treatment, baseline, and center as covariance for analysis of CFB; repeated measure logistic regression model with treatment and baseline as covariance for analysis of SPID3; Cochran-Mantel-Haenszel test, controlling for center, for the analysis of patients' global evaluation of the study medication

Major eligibility criteria (as summarized by Dr. Charles Lee):

Inclusion criteria:

1. Male or female subjects of any race, at least 12 years of age
2. History of SAR involving one of the following symptoms: runny nose, itchy/watery/red eyes, nasal congestion, sneezing, itchy nose/throat/palate, allergy-associated headache, facial pain/pressure/discomfort
3. History of experiencing at least moderate headache and/or facial pain/pressure/discomfort which worsens during allergy season and responds to treatment with OTC analgesics or who have never been treated with OTC analgesics
4. Positive skin test to an aeroallergen prevalent during the current allergy study season
5. Score of at least "moderate" for baseline instantaneous allergy-associated headache and/or facial pain/pressure/discomfort
6. A sum of at least 48/108 for the previous six morning and evening reflective symptom score assessments completed during the run-in phase.

Exclusion criteria:

1. Women who were pregnant or nursing
2. Women of child-bearing potential who were not practicing a medically acceptable method of contraception
3. Significant nasal anatomic deformities or polyps causing obstruction or patients who had more than two operations to remove polyps or repair nasal sinus/passages
4. Upper or lower respiratory tract infection within 14 days of screening
5. Persistently colored nasal discharge or diagnosis of acute or chronic sinusitis
6. History of rhinitis medicamentosa within 6 months of enrollment
7. Patients with asthma requiring corticosteroid (systemic, inhaled, or topical) or antileukotriene treatment
8. Subjects with a history of experiencing moderate to severe chronic tension headaches (>15/month) within 6 months of enrollment
9. Chronic NSAID therapy, defined as taking a daily (5 to 7 days per week) regimen of prescription NSAIDs or prescription doses of OTC NSAIDs. Aspirin therapy (up to 325 mg per day) for cardiac prophylaxis was to be permitted.
10. Patients who had taken any of the following medications within the corresponding washout period prior to taking the first dose of study medication

Washout time	Medication
6 hours	Oral immediate-release analgesics
12 hours	Sodium naproxen; Intranasal saline
24 hours	Oral sustained-release analgesics and COC-2 inhibitors; Topical, ocular, and nasal decongestants
3 days	Pseudoephedrine; Ocular antihistamines and NSAIDS; Herbal SAR medication
5 days	Hydroxyzine, loratadine, fexofenadine, cetirizine; Other oral antihistamines, all forms; Topical azelastine
14 days	Leukotriene inhibitors; Cromolyn sodium; Intranasal and ocular corticosteroids;
30 days	Systemic, oral, inhaled, and topical corticosteroids
90 days	Astemizole

6.2.2. Subject Disposition (Study AD-99-02)

6.2.2.1 Demographic and other baseline characteristics

The sample population consisted of 1070 subjects who took at least one dose of the study medication with an age range of 12 to 85 years and a mean of 34 years, 14% youngster (age <18 years), 62% adults age 18 to <45 years, 22% adults age 45 to <65 years, and 2% elderly (age ≥65 years); 71% females; 79% Caucasian, 11% African American, 8% Hispanic, 1% Asian, and 1% others. The distribution of the demographic sub-group in the study population was similar to what has been commonly observed in the clinical trials except that there was not enough effort to include more elderly subjects. The treatment groups were comparable with regard to the demographic characteristics such as age, race, and gender. The treatment groups were also comparable in terms of the total and the individual allergy symptom scores at baseline, and with regard to baseline pain intensity (65% to 66% had moderate and 34% to 35% had severe pain at baseline).

6.2.2.2. Drug exposure and study execution

Of the 1070 subjects who received at least one dose of the study medication
- 269 received 2 tablets of the triple combination of ibuprofen 400mg, pseudoephedrine 60mg, and chlorpheniramine 4mg (I/P/C 2-cap);
- 263 received one tablet of the triple combination (I/P/C 1-cap);
- 273 received one tablet of the double combination of pseudoephedrine 30mg and chlorpheniramine 2mg, i.e., the combination without ibuprofen (P/C 1-tab);
- 265 received placebo.

As shown in table 3 at least 97% of the subjects in each treatment group received at least 19 doses of the study drug. At least 84% of each group received either 20 or 21 doses, indicating adequate patient compliance. The treatment groups were comparable in terms of dosing distribution. The group mean and group median number of doses taken during the course were the same for all treatment groups.

About 10 to 11% subjects had an early termination as shown in table 4, mostly due to protocol violation (8%) and adverse events (1 to 2%). The types of protocol violations were missing dosing times/amounts, deviation from scheduled time of pain assessment, missing pre-dosing pain assessment or overall assessment, pre-dosing pain assessment beyond 5 minutes post-dose, missing day 1 reflective assessment, missing days 2-7 reflective assessments, overall assessment beyond 12 hours past last dose, etc. A few subjects were terminated early from the study for the reasons of treatment failure, lost to follow-up, withdrawal of consent, and

administrative or other reasons. There were no remarkable treatment group differences in terms of the reasons for early termination.

Intention-to-treat (ITT) population for efficacy analysis conducted by the Sponsor consisted of 1044 (97.6%) of the 1070 subjects randomized as shown in table 4. Up to 3% were excluded in each treatment group, mostly for protocol violations as described above. The exclusion of these subjects in the Sponsor's primary analysis had not affected the results of the analysis using all randomized subjects as the ITT population as confirmed by the statistical reviewer Dr. Choi's sensitivity analysis.

Table 3. Drug exposure (Study AD-99-02)

Total doses	***I/P/C 2-cap N= 269***	***I/P/C 1-cap N= 263***	***P/C 1-tab N= 273***	***Placebo N= 265***	***Total N= 1070***
1-15	5 (2%)	7 (3%)	9 (3%)	6 (2%)	27 (3%)
19	22 (8%)	34 (13%)	35 (13%)	31 (12%)	122 (11%)
20	129 (48%)	114 (43%)	120 (44%)	117 (44%)	480 (45%)
21	113 (42%)	108 (41%)	109 (40%)	111 (42%)	441 (41%)
Mean	20	20	20	20	20
STD	2.1	2.7	2.6	2.1	2.4
Median	20	20	20	20	20

Table 4. Reasons for early termination and for exclusion from ITT analysis

	I/P/C 2-cap N= 269	***I/P/C 1-cap N= 263***	***P/C 1-tab N= 273***	***Placebo N= 265***	***Total N= 1070***
# early termination	30 (11.2%)	27 (10.3%)	28 (10.3%)	28 (10.6%)	113 (10.6%)
The number (%) of early termination due to the following reasons					
Protocol violation	21 (7.8%)	20 (7.6%)	21 (7.7%)	22 (8.3%)	84 (7.9%)
Adverse event	6 (2.2%)	3 (1.1%)	5 (1.8%)	4 (1.5%)	18 (1.7%)
Treatment failure	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.8%)	5 (0.5%)
Lost to follow-up	0	2 (0.8%)	0	0	2 (0.2%)
Withdrew consent	0	0	1 (0.4%)	0	1 (0.1%)
Administrative/other	2 (0.7%)	1 (0.4%)	0	0	3 (0.3%)
ITT subjects	**265**	**256**	**266**	**257**	**1044**
# not in ITT analysis	4 (1.5%)	7 (2.7%)	7 (2.6%)	8 (3.0%)	26 (2.4%)
The number of exclusion from ITT analysis due to the following reasons					
Protocol violation	1	4	7	8	20
Adverse event	1	0	0	0	1
Lost to follow-up	0	2	0	0	2
Administrative/other	2	1	0	0	3

6.2.3. Discussion of Efficacy Results (study AD-99-02)

6.2.3.1. Contribution by ibuprofen

As shown in table 5 the triple combination with ibuprofen (I/P/C 1-cap) performed statistically better ($p<0.001$) than the double combination without ibuprofen (P/C 1-tab), whereas no statistically significant separation was shown between the double combination (P/C 1-tab) and placebo, in terms of the pain scores measured by SPID3. The finding strongly suggested the contribution of ibuprofen to the analgesic effect of the treatment. In addition, the triple combination (I/P/C 1-cap) performed statistically better ($p=0.007$) than the double combination (P/C 1-tab), which in turn performed statistically better ($p=0.044$) than placebo, in terms of the instantaneous pre-dose pain measured three times a day over 7 days as shown in table 5. The findings suggested that the combination without ibuprofen had a effect on allergy-associated pain and the inclusion of ibuprofen in the combination provided significantly additional beneficial treatment effect on the relief of allergy-associated pain upon repeated dosing. The statistical significance of the treatment differences has been very valuable in assessment of treatment effects and will be considered together with clinically significant effect size when the criteria for the latter can be established in the near future.

6.2.3.2. Contribution by chlorpheniramine 2mg

Ideally, the component contribution of chlorpheniramine 2mg to the antihistamine effect should be evaluated by comparing the combinations with and without 2mg of chlorpheniramine. However, the treatment arm without chlorpheniramine 2mg was not included in the study design. The two combinations containing chlorpheniramine 2mg (I/P/C 1-cap and P/C 1-tab) in this study were both shown (table 5) to be significantly superior to placebo in terms of the overall average of total symptoms (OATSS) and the overall average of total antihistamine symptoms (OATASS). The findings supported the effect of chlorpheniramine 2mg, as being used together with the other two active ingredients of the triple combination, in treating the total allergy-related symptoms and antihistamine-specific symptoms.

6.2.3.3. The minimum effective dose and dose response

The minimum effective dose of the triple combination was suggested by the demonstration of statistically significant superiority ($p<0.001$) of I/P/C 1-cap to placebo in the primary (OATSS) and all secondary efficacy parameters measured (table 5 and table 6). The triple combination at two-tablet dose level had the same treatment effects as that of one tablet in comparison to placebo. There were no

statistically significant separations between the one-tablet and two-tablet doses of the triple combination in any of the primary or secondary efficacy parameters studied. The efficacy findings suggested that one-tablet dose should be recommended, instead of dosing with one or two tablets as commonly seen in the OCT labeling of the products containing similar ingredients.

Table 5. Primary and key secondary efficacy parameters (study AD-99-02)

Treatment comparison	*Treatment differences*				
	I/P/C 2-cap > Placebo	*I/P/C 1-cap > Placebo*	*P/C 1-tab > Placebo*	*I/P/C 1-cap > P/C 1-tab*	*I/P/C 2-cap > I/P/C 1-cap*
Pain - SPID3					
Treatment difference	0.86	0.75	0.10	0.65	0.11
95% confidence interval	(0.50, 1.22)	(0.39, 1.11)	(-0.26, 0.46)	(0.29, 1.01)	(-0.25, 0.47)
p-value	< 0.001	< 0.001	0.583	< 0.001	0.553
Overall average of total symptom scores - OATSS					
Treatment difference	1.76	1.51	0.75	0.76	0.25
95% confidence interval	(1.20, 2.32)	(0.95, 2.07)	(0.19, 1.30)	(0.21, 1.32)	(-0.31, 0.81)
p-value	< 0.001	< 0.001	0.009	0.007	0.376
Overall average of total antihistamine scores - OATASS					
Treatment difference	0.92	0.80	0.43	0.37	0.13
95% confidence interval	(0.64, 1.21)	(0.51, 1.09)	(0.14, 0.72)	(0.08, 0.65)	(-0.16, 0.41)
p-value	< 0.001	< 0.001	0.003	0.012	0.390

Note:

- SPID3 is the time-weighted sum of the pain intensity difference at 2 and 3 hours after the initial dose;

- OATSS is the change from baseline in the overall average reflective total symptom scores, derived from averaging over 7 days, of the 7 daily average of the AM and PM total scores of 6 symptoms: nasal congestion, sneezing, rhinorrhea (runny nose), itchy nose/throat/palate, itchy/watery/red eyes, pain (headache and/or facial pain/pressure discomfort);

- OATASS is the change from baseline in the overall average reflective total antihistamine scores, derived similarly as above based on only the antihistamine symptoms: sneezing, itchy/watery/red eyes, itchy nose/throat/palate.

Table 6. Other secondary efficacy parameters (study AD-99-02)

	Statistically significant treatment differences				
Change from baseline	*I/P/C 2-cap > Placebo*	*I/P/C 1-cap > Placebo*	*P/C 1-tab > Placebo*	*I/P/C 1-cap > P/C 1-tab*	*I/P/C 2-cap > I/P/C 1-cap*
1. AM overall average of total symptoms	p< 0.001	p< 0.001	P=0.024	P=0.041	No
2. PM overall average of total symptoms	p< 0.001	p< 0.001	P=0.005	P=0.005	No
3. Daily average of total symptoms (each of 7 days)	p< 0.001	p< 0.001	p< 0.05 (on day 2, 3, 4, 5, 7)	p< 0.05 (on day 1, 2, 3, 6)	No
4. Daily average of antihistamine symptoms	p< 0.001	p< 0.001	p< 0.05 (except day 1)	p< 0.05 (on day 1, 2, 3)	No
5. Overall average of individual symptoms					
Nasal congestion	p< 0.001	p< 0.001	No	No	No
Sneezing	p< 0.001	p< 0.001	p< 0.001	P=0.022	No
Runny nose	p< 0.001	p< 0.001	No	P=0.043	No
Itchy nose/throat/palate	p< 0.001	p< 0.001	P=0.017	No	No
Itchy/watery/red eyes	p< 0.001	p< 0.001	P=0.040	P=0.009	No
6. Pre-dosing pain	p< 0.001	p< 0.001	P=0.044	P=0.007	No
7. Overall evaluation	p< 0.001	p< 0.001	p< 0.001	No	No

Note:
1 (or 2). Change from baseline in the AM (or PM) overall total reflective symptom scores, derived by averaging the total score of 6 symptoms over 7 mornings (or 7 evenings);
3. Change from baseline in the average reflective total symptom score (ATSS) for each treatment day (days 1-7), derived from the daily average of the AM and PM total scores of 6 symptoms;
4. Change from baseline in the average reflective total antihistamine symptoms score for each treatment day, derived similarly as above but included only the antihistamine symptoms;
5. Change from baseline in the overall average individual reflective symptom scores (except for pain), derived from averaging over 7 days, of the daily average of the AM and PM individual symptom scores;
6. Incidence of pre-dose instantaneous allergy-associated pain (excluding the baseline measurement), using the repeated measure logistic regression model.
7. The overall evaluation of study medication (patients' global).

6.3. Efficacy Conclusions

(Refer to table 5 and table 6 and the discussions above for detail)

The triple combination at both one-tablet (200mg/30mg/2mg) and 2-tablet (400mg/60mg/4mg) dose levels was demonstrated to be efficacious as measured by statistically significantly better ($p<0.001$) performance than placebo in terms of the primary and all the secondary efficacy parameters. The minimum effective dose was demonstrated to be the one-tablet dose. Also, there were no statistically significant separations between the one-tablet and 2-tablet doses of the triple combination in any of the efficacy parameters studied, suggesting the lack of dose response between the two dose levels. The efficacy findings of no additional beneficial effect from the 2-tablet dose supported the recommendation of one tablet only for the OTC labeling.

Ibuprofen was shown to contribute to the analgesic effect of the triple combination on relieving allergy-associated pain. The combination with ibuprofen had significantly better statistical performance than the combination without ibuprofen as measured by SPID3 after the initial dose and by the parameter defined as the incidence of pre-dose pain measured 3 times a day over the seven day treatment period.

Chlorpheniramine 2mg when being used together with ibuprofen and pseudoephedrine had an effect on relieving antihistamine-related symptoms at a level lower than what had been defined in the OTC Monograph. The combinations containing chlorpheniramine 2mg (with and without ibuprofen) had statistically significantly better performance than placebo in terms of the overall average of total symptom scores (OATSS) and the overall average of total antihistamine symptoms (OATASS).

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

In the multiple-dose safety study (AD-99-02) of more than 500 subjects, who had continuous exposure to the triple combination up to 3 times a day for up to 7 days, the total number of subjects reporting AEs in the one-tablet group (24%) was similar to that of the placebo group (20%). There were dose-related (one tablet to two tablets of the triple combination) increase in the total number of subjects reporting AEs and in the most frequently reported AEs such as somnolence, dizziness, dry mouth, dyspepsia, insomnia, and asthenia, which were known to be the most common AEs associated with the therapeutic doses of the three individual ingredients. There were no serious events or deaths and only a relatively small percentage (≤2%) of withdrawal due to AEs. The addition of ibuprofen to the combination at 200mg level was not shown to increase AE incidence (refer to discussions in section 7.3.1.6 for detail). The incidence of AE was too low in the single-dose PK studies (AD-99-01 and AD-99-03) to provide useful information for the treatment comparison.

There were no new safety signals for the individual ingredients based on the review of safety information from post-marketing surveillance and literature (refer to discussions in section 7.4). The safety information on the concurrent use of the products containing one or more than one of the three active ingredients was very limited for various possible reasons (refer to section 7.5 and 7.6 for detail). The review of post-marketing surveillance data on serious cases reported with the concurrent use of the 3 active ingredients suggested a need for the OTC review division to study the extent of the concurrent use of multiple OTC cold/flu products containing the same or similar ingredients in the OTC population and the magnitude of its associated risks.

7.2. Description of Patient Exposure

As shown in table 1, table 3, and table 9, a total of 573 subjects were exposed to the triple combination in the 3 clinical studies, 41 of 573 subjects in the two single-dose PK studies (AD-99-01 and AD-99-03) and 532 of 573 in the 7-day multiple-dose study (AD-99-02). The longest exposure was 21 doses in 221 subjects and the highest level of exposure was the 2-tablet dose taken by 310 subjects in the 3 clinical trials. In the multiple dose study of 7 days in duration 264 of the 520 subjects taking at least 19 doses were exposed to the 2-tablet dose level.

7.3. Safety Findings from Clinical Studies

7.3.1. Multiple-Dose Study (AD-99-02)

7.3.1.1. Incidence of adverse events

Adverse events (AE) were reported in 42% subjects on 2-tablet dose of the triple combination (I/P/C 2-cap), 24% on one-tablet dose of the triple combination (I/P/C 1-cap), 25% on one-tablet dose of double combination (P/C 1-tab), and 20% on placebo. The two active treatment arms (with and without ibuprofen) dosed at one tablet had AE incidence similar to that of placebo. The doubling of the dose of the triple combination from one tablet to 2 tablets increased the incidence of total AE from 24% to 42% (a 75% increase). Most adverse events were rated as mild or moderate in severity (70 to 85% of events in various treatment groups).

The most commonly reported (≥2%) adverse events per treatment group are summarized based on body system in table 6 below and will be discussed in the later sections.

Table 7. Most frequently reported AE in the multiple-dose study (AD-99-02)

	Number (%) of Subjects with AE			
Treatment arm	***I/P/C 2-cap***	***I/P/C 1-cap***	***P/C 1-tab***	***Placebo***
Number of subjects	N=269	n=263	n=273	n=265
Adverse experiences counts	179	91	99	81
Total #subjects with AE	**114 (42.4%)**	**63 (24.0%)**	**69 (25.3)**	**53 (20.0%)**
Nervous system	*76 (28.3%)*	*42 (16.0%)*	*37 (13.6%)*	*11 (4.2%)*
Somnolence	44 (16.4%)	24 (9.1%)	23 (8.4%)	5 (1.9%)
Dry mouth	15 (5.6%)	9 (3.4%)	10 (3.7%)	2 (0.8%)
Dizziness	16 (5.9%)	5 (1.9%)	4 (1.5%)	6 (2.3%)
Insomnia	9 (3.3%)	4 (1.5%)	4 (1.5%)	1 (0.4%)
Body as a Whole	*24 (8.9%)*	*11 (4.2%)*	*10 (3.7%)*	*15 (5.7%)*
Headache	8 (3.0%)	2 (0.8%)	2 (0.7%)	3 (1.1%)
Asthenia	11 (4.1%)	3 (1.1%)	0	0
Digestive system	*27 (10.0%)*	*12 (4.6%)*	*23 (8.4%)*	*17 (6.4%)*
Dyspepsia	14 (5.2%)	5 (1.9%)	6 (2.2%)	9 (3.4%)
Nausea	6 (2.2%)	2 (0.8%)	8 (2.9%)	5 (1.9%)
Respiratory system	13 (4.8%)	6 (2.3%)	8 (2.9%)	9 (3.4%)
Pharyngitis	9 (3.3%)	2 (0.8%)	3 (1.1%)	6 (2.3%)

7.3.1.2. Serious adverse events

There was no serious AE in the exposed population and no reports of death.

7.3.1.3. Early termination due to AEs

As shown in table 4 few subjects were terminated early due to adverse events: 6 (2.2%) subjects on I/P/C 2-cap, 3 (1.1%) on I/P/C 1-cap, 5 (1.8%) on P/C 1-tab, and 4 (1.5%) on placebo. The most noticeable individual event as the cause of early termination was somnolence, which occurred in 3 of the 6 subjects terminated on I/P/C 2-cap, 2 of the 5 subjects on P/C 1-tab, and none of the subjects on I/P/C 1-cap or placebo. The finding was consistent with what was known about chlorpheniramine since somnolence is a manifestation of the CNS depression by the first generation H_1 antagonists and reported to be the most frequent adverse event accompanying therapeutic dose of drugs in the class (Goodman and Gilman's the Pharmacological Basis of Therapeutics).

7.3.1.4. Triple combination in comparison to placebo

As shown in table 7, there were noticeably more cases of somnolence, dry mouth, insomnia, and asthenia reported in both the one-tablet and two-tablet triple combination groups than in the placebo group. These events were known to be associated with the therapeutic use of the first generation H_1 antagonists due to the effects of CNS depression (somnolence and asthenia), CNS excitation (insomnia), and antimuscarinic action (dry mouth). The CNS sedative effect of the first generation H_1 antagonists has been reported as more pronounced in a sub-group represented by diphenhydramine. Somnolence was reported in 50% of those treated with its therapeutic dose. Diphenhydramine was even used as an OTC sleep aid in addition to its use OTC as antihistamine. The sympathomimetic effects of pseudoephedrine on CNS were also manifested as insomnia and asthenia.

7.3.1.5. Dose response in AE

Increased incidences of somnolence (9.1 to 16.4%), dry mouth (3.4 to 5.6%), dizziness (1.9 to 5.9%), insomnia (1.5 to 3.3%), headache (0.8 to 3.0%), asthenia (1.1 to 4.1%), and dyspepsia (1.9 to 5.2%) were reported when the one-tablet group was compared to the two-tablet group of the triple combination (table 7). There were more cases of early termination due to somnolence in the two-tablet group than the one-tablet group as discussed in the section 7.3.1.3. The findings suggested dose-related increase in toxicity and further supported the limit of dose to one tablet for OTC use of this triple combination product.

7.3.1.6. Contribution of ibuprofen to the AE incidence

The AE incidence was very similar for the groups treated with one tablet of the combinations with (I/P/C 1-cap) and without ibuprofen (P/C 1-tab). As shown in table 7 the only noticeable differences were 1.1% asthenia in the I/P/C 1-cap group versus none in the P/C 1-tab group and 0.8% nausea in the I/P/C 1-cap group versus 2.9% in the P/C 1-tab group (1.9% in the placebo group). The data did not suggest that the addition of ibuprofen lead to an increase in GI irritation at one-tablet level. Gastrointestinal AEs have been commonly reported with the use of the single-ingredient product for each of the 3 active ingredients. The expected GI AEs theoretically would be much higher when the 3 ingredients are used together. However, GI events (total and the most frequently reported individual events) were not dramatically different when the triple combination groups were compared to placebo in this study. GI events were lower in subjects on I/P/C 1-cap than placebo and less than 2-fold higher in subjects on I/P/C 2-cap than placebo.

7.3.1.7. AE with respect to demographic characteristics

The study population consisted of 14% youngster (age <18 years), 62% adults age 18 to <45 years, 22% adults age 45 to <65 years, and 2% elderly (age ≥65 years); 71% females; 79% Caucasian, 11% African American, 8% Hispanic, 1% Asian, and 1% others. The elderly and the minority groups did not have sufficient group size to allow valid comparisons (grouping ethnic minorities together would not yield useful information). As shown in table 8 the same trend of dose-related increase in reports of somnolence, dizziness, dry mouth, asthenia was observed when dose increased from placebo to one-tablet of triple combination and then to two-tablet of triple combination for most of the demographic subgroups.

In terms of the total number of subjects with any AEs, the youngest age group reported less AEs per treatment arm than the three older age groups (refer to table 8 for detail). Elderly would be expected to report more treatment-related AEs especially in terms of somnolence and dizziness. However, the comparison of the AE reporting between the elderly and non-elderly could not be made since only few elderly subjects were included in the study (refer to section 9 for discussions on adequacy of analysis).

In terms of the total number of subjects with any AE males reported less AEs per treatment arms than females (refer to table 8 for detail).

In terms of the individual AE with respect to each demographic characteristic there were variations per age-treatment strata and per gender-treatment strata due to

small subgroup sample size as shown in table 8. Therefore, no valid conclusions could be made because of the limited data sets.

7.3.1.8. Drug-drug interactions and drug-disease interactions

Other than those medical conditions and concomitant medication listed in the exclusion criteria subjects were not limited in having other medical conditions or taking other medications (for the purpose of having a study population more representative of the general population). Because the trial was not designed to study the specific drug-drug interactions between the triple combination and other commonly used medications or drug-disease interactions, the wide variation in the use of concomitant medication and in having concurrent medical conditions in study AD-99-02 made the data not interpretable with regard to these interactions.

Table 8. AE with respect to demographic characteristics (Study AD-99-02)

	Number (%) of Subjects with AE			
Treatment arm	***I/P/C 2-cap***	***I/P/C 1-cap***	***P/C 1-tab***	***Placebo***
12 < 18 y.o.	**(n=35, or 13%)**	**(n=39, or 15%)**	**(n=36, or 13%)**	**(n=39, or 15%)**
Any AE	10(28.6%)	6(15.4%)	6(16.7%)	5(12.8%)
Somnolence	6(17.1%)	3(7.7%)	1(2.8%)	0
Dizziness	2(5.7%)	1(2.6%)	0	1(2.6%)
Dry Mouth	2(5.7%)	1(2.6%)	0	0
Asthenia	1(2.9%)	1(2.6%)	0	0
18 < 45 yrs	**(n=174, or 65%)**	**(n=157, or 60%)**	**(n=173, or 63%)**	**(n=163, or 62%)**
Any AE	78(44.8%)	39(24.8%)	50(28.9%)	33(20.2%)
Somnolence	32(18.4%)	16(10.2%)	18(10.4%)	4(2.5%)
Dizziness	10(5.7%)	2(1.3%)	4(2.3%)	4(2.5%)
Dry Mouth	10(5.7%)	3(1.9%)	7(4.0%)	2(1.2%)
Asthenia	8(4.6%)	2(1.3%)	0	0
45 < 65 yrs	**(n=56, or 21%)**	**(n=62, or 24%)**	**(n=58, or 22%)**	**(n=60, or 23%)**
Any AE	25(44.6%)	16(25.8%)	12(20.7%)	14(23.3%)
Somnolence	6(10.7%)	5(8.1%)	4(6.9%)	1(1.7%)
Dizziness	4(7.1%)	2(3.2%)	0	1(1.7%)
Dry Mouth	2(3.6%)	4(6.5%)	3(5.2%)	0
Asthenia	2(3.6%)	0	0	0
≥65 yrs	**(n=4, or 1%)**	**(n=5, or 2%)**	**(n=6, or 2%)**	**(n=3, or 1%)**
Any AE	1(25.0%)	2(40.0%)	1(16.7%)	1(33.3%)
Somnolence	0	0	0	0
Dizziness	0	0	0	0
Dry Mouth	1(25.0%)	1(20.0%)	0	0
Asthenia	0	0	0	0
Males	**(n=80, or 30%)**	**(n=74, or 28%)**	**(n=80, or 29%)**	**(n=74, or 28%)**
Any AE	28(35.0%)	6(8.1%)	11(13.8%)	10(13.5%)
Somnolence	19(23.8%)	1(1.4%)	4(5.0%)	2(2.7%)
Dizziness	2(2.5%)	1(1.4%)	0(0.0%)	2(2.7%)
Dry Mouth	2(2.5%)	0	1(1.3%)	1(1.4%)
Asthenia	3(3.8%)	1(1.4%)	0	0
Females	**(n=189)**	**(n=189)**	**(n=193)**	**(n=191)**
Any AE	86(45.5%)	57(30.2%)	58(30.1%)	43(22.5%)
Somnolence	25(13.2%)	23(12.2%)	19(9.8%)	3(1.6%)
Dizziness	14(7.4%)	4(2.1%)	4(2.1%)	
Dry Mouth	13(6.9%)	9(4.8%)	9(4.7%)	
Asthenia	8(4.2%)	2(1.1%)	0	

7.3.2. Single-Dose Study

There were two single-dose PK studies of crossover design in which a single two-tablet dose of the triple combination was given to 29 subjects in drug interaction study (AD-99-03) and to 12 subjects twice (with a one-week washout period) in the food study (AD-99-01).

7.3.2.1. Adverse events

In food effect study (AD-99-01), adverse events (AEs) were reported in 2 of 12 (17%) subjects. There was only one report for each of the following symptoms: asthenia, nausea, and syncope.

In the PK drug interaction study (AD-99-03), 6 of the 29 (21%) subjects on triple combination reported AEs, in comparison to 2 of 28 (7%) on ibuprofen 400mg, 4 of 28 (14%) on pseudoephedrine 60mg, and 3 of 28 (11%) on chlorpheniramine 4mg. Each of the following AEs occurred only once in subjects receiving the triple combination: somnolence, dizziness, asthenia, headache, injection site reaction, nausea, anorexia, and rash as shown in table 9.

All AEs were rated as mild except that syncope was rated as moderate in severity. There were no serious AEs, reports of death, or early terminations due to AEs. The type of AE reported in the PK studies was similar to the type of the most frequently reported AEs in the multiple-dose study (AD-99-02).

In this reviewer's opinion single-dose safety data were limited in their usefulness for the treatment group comparisons because of the low frequency of AE occurrence.

Table 9. AE reported in the single-dose PK studies (AD-99-01 and AD-99-03)

	Number (%) of Subjects with AE				
Study	***AD-9901***	***AD-9903***			
Treatment	***Ibu/pse/chl 400/60/4mg***	***Ibu/pse/chl 400/60/4mg***	***Ibuprofen 400mg***	***Pse 60 mg***	***Chl 4mg***
Number of subjects	***(n=12)***	***(n=29)***	***(n=28)***	***(n=28)***	***(n=28)***
# adverse events	3	8	2	6	4
# subjects with AE	2 (16.7)	6 (20.7)	2 (7.1)	4 (14.3)	3 (10.7)
Somnolence	0	1 (3.4)	0	0	1 (3.6)
Dizziness	0	1 (3.4)	0	0	1 (3.6)
Asthenia	1 (8.3)	1 (3.4)	0	0	0
Headache	0	1 (3.4)	1 (3.6)	1 (3.6)	1 (3.6)
Injection site reaction	0	1 (3.4)	0	0	1 (3.6)
Nausea	1 (8.3)	1 (3.4)	0	1 (3.6)	0
Anorexia	0	1 (3.4)	0	1 (3.6)	0
Vomiting	0	0	0	1 (3.6)	0
Syncope	1 (8.3)	0	0	0	0
Pharyngitis	0	0	1 (3.6)	0	0
Rhinitis	0	0	0	1 (3.6)	0
Pruritus	0	0	0	1 (3.6)	0
Rash	0	1 (3.4)	0	0	0

7.4. Safety of Individual Ingredients

The safety update on ibuprofen and pseudoephedrine (when the 2 ingredients were used alone, used together, or used in a combination) were thoroughly reviewed by Dr. Andrea Leonard-Segal of the OTC Division (refer to the clinical review of NDA 21-374 dated April 26, 2002 for detail). Based on her review of the safety information from post-marketing surveillance and literature her conclusion was that there were no new significant safety signals with the use of the combination of ibuprofen and pseudoephedrine and that the OTC use of the combination in accordance with the labeling directions was not considered unsafe.

Chlorpheniramine is generally recognized as safe and effective for over-the-counter (OTC) use as an individual or combination antihistamine ingredient in doses between 16mg and 24mg per day (21 CFR 341.72(d)(3)). The single ingredient is available OTC at 4mg, 8mg, and 12mg (extended-release) as a single dose to be used as antihistamine. Post-marketing surveillance data were not considered useful for the safety evaluation of chlorpheniramine in this reviewer's opinion because of under reporting that the monograph products were not required to report treatment-related AEs (per conversation with OTC review division). Also, chlorpheniramine was used mostly with other active ingredients in cold/flu drug combinations, which would make the data (which were already of very poor quality) very difficult to interpret. The literature search on the safety of chlorpheniramine used alone or in a combination was based on MEDLINE, EMBASE (Alert), EMBASE, BIOSIS REVIEWS, Derwent Drug File, and SciSearch database with no time limitation. As summarized in table 10 there were very few literature reports generated from so many years (at least more than 30 years) of OTC use of the products containing chlorpheniramine. The remarkable findings are hematological complications, allergic reactions, drug-drug interactions with antipsychotic drugs, anticonvulsants, cocaine, antiviral drugs, and glycyrrhizin (the major ingredient in licorice). Allergic reactions (especially with topical use of antihistamine), psychosis, seizures, and rare hematological complications serious in nature were known adverse events associated with the use of antihistamine as recorded in the drug information text books (e.g., AHFS Drug Information, Goodman and Gilman's the Pharmacological Basis of Therapeutics).

Table 10. Literature review of the chlorpheniramine containing products

Source	*Patient*	*Chlorpheniramine exposure*	*Adverse events and outcomes*
Strauss 1989	27 yo male cocaine abuser	Large amount in a combination with phenylpropanolamine	Psychosis (possible drug interaction of antihistamine with cocaine)
Serra et al 1996	Healthy adult males	Single dose 4mg	Influence of cognitive ability by decreasing the end phase of the mismatch negativity portion of the auditory event-related potentials
Levine et al 1993	19 yo male	Overdose of combination drugs containing chlorpheniramine 2mg	Multiple drug intoxication leading to death where chlorpheniramine concentration was 2.6mg/L in heart blood and 8.9 mg/kg in liver and was not considered significantly elevated.
Philpot et al 1993	Healthy pilots	4mg twice daily for 3 days	Fatigue, drowsiness, lethargy, dry mouth, or headache were reported in 5 of 11 subjects but no flying impairment.
Shanon et al 1993	8 to 12 yo 13 to 16 yo	2mg four times a day 4mg four times a day	School performance not impaired
Hayashi et al 2001	71 yo male	Topical combination product containing chlorpheniramine	Local reaction described as itchy erythematous lesion, with seropapules and erosions, with patch test positive for chlorpheniramine
Demoly et al 2000	57 yo female	Dexchlorpheniramine 2mg	Generalized urticaria with negative results to dexchlorpheniramine on subsequent allergy skin tests
Brenner et al 1990	56 yo female	OTC combination product containing chlorpheniramine	Pemphigus vulgaris induced by the combination product in a subject who had genetic predisposition for pemphigus (her 60 years old sister had pemphigus erythematosus for the past 4 years).
Hardin 1988	48 yo female	OTC combination product containing chlorpheniramine	Drug-induced agranulocytosis (Schultz syndrome) leading to death in a critically ill patient
Duran-Suarez 1981	48 yo female	Dexchlorpheniramine 4mg/day for 3 days	Drug-induced hemolytic anemia, improved with treatment of blood transfusion and prednisone.
Kanoh et al 1977	51 yo male	6mg/day for 3-4 days a week	Drug-induced aplastic anemia, improved with treatment of anabolic steroid and corticosteroid.
Deringer, Maniatis 1976	32 yo female	Unknown amount for 1 month and then for 3-4 days a year later	Thrombocytopenia which recurred when the patient took the drug a year later.
Eisner et al 1975	53 yo male	OTC combination containing chlorpheniramine	Drug-induced thrombocytopenic purpura confirmed by the presence of a drug-dependent IgG antiplatelet antibody.
Chouinard et al 1978	27 yo female	One Contact-C capsule (chlorpheniramine is an ingredient)	Suspected drug-drug reaction with antipsychotic drugs in a patient with severe schizophrenia who had a history of EKG abnormality associated with chlorpromazine treatment at 900 mg/d. The event of ventricular fibrillation lead to death.
Kuwatsuru et al 1991	15 yo male	One dose of chlorpheniramine i.v.	Suspected drug-drug reaction with i.v. glycyrrhizin, which was reported as headache, nausea, and vomiting.
Pugh, Geddes 1975	17 yo female	4mg q.i.d.	Drug-drug reaction that lead to toxic levels of anticonvulsants and associated neurological symptoms
Millet et al 1982	52 adult volunteers	chlorpheniramine 4mg amantadine 100 mg, rimantadine 100 mg, amantadine + chlorpheniramine placebo	More adverse events of dizziness, fatigue, and dry Mouth reported in the group treated with drug combination of amantadine and chlorpheniramine but not the cognitive performance

7.5. Literature Review - the Concurrent Use of the Three Active Ingredients

There were no literature reports with regard to the concurrent use of ibuprofen, pseudoephedrine, and ibuprofen containing products. This could be due to multiple factors such as market unavailability of the triple combination products containing ibuprofen, the availability of other similar products of the same drug categories, low need for the use of such combination, lack of interest in studying such combination, rare occurrence of significant AEs at OTC dosing levels, etc.

7.6. Post-Marketing Surveillance

The interpretation of safety based on surveillance data could be misleading for many reasons. Adverse events were not all reported especially for monograph products (no requirement for reporting) and exposure information was not available to allow a prediction on risk ratio. The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of the product, the year of marketing, publicity, nature of reactions, and other factors which vary over time, from product to product, and country to country. The detailed information on the time sequence of events and the relationship between the sequence of events and time course of drug exposure are usually not available to allow an adequate assessment of causal effect of suspected agent on the event of interest. A given reaction may be due to underlying disease, concomitant medication, or other causes.

Surveillance data in general might have some value in providing clues as to the trend of events or the occurrence of rare events but not considered useful at all for evaluating whether there would be an increased risk associated with the concurrent use of several active ingredients as compare to the risk associated with the use of single-ingredient products. Only a very large trial with a full factorial design could provide useful data to address the issue.

7.6.1. Case Reports

There was only a very small (relative to how widely in use of the products containing one or more than one of the 3 ingredients discussed here) number of cases on the concurrent use of all three ingredients in the post-marketing surveillance database. A total of 101 case reports were located in the three main databases: the Sponsor's AE database, the FDA SRS database, and the FDA AERS database. Of these case reports 26 (3 of 26 were duplicate cases) were considered as serious (resulted in death, was life threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in a persistent or significant

disability or incapacity, or resulted in a congenital anomaly or birth defect). Three of the serious cases (1 of 3 was a duplicate case) were suspected to be related to the concurrent use of the three active ingredients.

Table 11. Number of cases on the concurrent use of three active ingredients (ibuprofen, pseudoephedrine, and chlorpheniramine)

	Number of AE on concurrent use of three active ingredients			
Database	*Sponsor*	*FDA SRS*	*FDA AERS*	*Total*
AE	16	58	27	101
Serious AE	4	13	9	26
Triple combo suspected as the cause of serious AE	0	3	0	3

7.6.2. Serious Adverse Events

The cases of serious AE were summarized in table 12 in terms of suspected medication, concomitant medication, adverse events, and outcomes.

There were 6 fatal cases. The first case was a 9-year-old female who had a history of Batten's disease (late infantile neuronal ceroid lipofuscinosis) and respiratory insufficiency with oxygen dependency. She was in a critical condition one year ago and had two hospitalizations for hypoxia/pneumonia and worsening seizures in the previous month. She was hospitalized again for respiratory insufficiency while enrolled in a study of Zonegran (zonisamide) for the control of her seizure, and subsequently, had elevated LFTs, sepsis, multi-system organ failure, and died. The episodes of elevated LFTs and multi-system organ failure were thought to be associated with Zonegran based on the investigator's assessment. Among the long list of concomitant medication were two ibuprofen products (Advil and Motrin) and two OTC cough/cold combination products containing both pseudoephedrine (Dimetane and Pediacare Cough-Cold) and antihistamine and one of the antihistamine ingredients was chlorpheniramine.

The second fatal case was a 19-year-old football player who took multiple OTC medication, including Tylenol, Advil, Aspirin, Nyquil (a combination of chlorpheniramine/dextromethorphan/pseudoephedrine), and Comtrex (a combination of acetaminophen/pseudoephedrine/chlorpheniramine), at unknown dosage for flu like symptoms. He presented at a local hospital with dehydration and thrombocytopenia and died suddenly a few hours after admission. Toxicology findings include detectable blood levels of acetaminophen, codeine, dextromethorphan (beyond therapeutic range), doxylamine, ibuprofen,

pseudoephedrine. These products or their metabolites, plus chlorpheniramine were also detected in his urine. Autopsy revealed extensive centrilobular hepatocellular necrosis and multifocal acute myocarditis (which was reported as complications of acute acetaminophen poisoning as described in Ellenhorn's Medical Toxicology, 1997) most consistent with acetaminophen poisoning.

The third fatal case was a female adult of unknown age who had a history of bipolar disorder, schizophrenia, and hepatitis C and was on maintenance treatment with clozapine for 5 years with quitiapine added to her regimen 2-3 weeks before the event. The patient presented to the ER septic and hypotensive, with a WBC count of $0.1 \times 10^{9}/L$. The admission diagnosis was circulatory collapse secondary to sepsis, right middle lobe pneumonia, and neutropenia. She was persistently septic and difficult to oxygenate and finally expired. Her concomitant medication included ibuprofen, Nyquil (chlorpheniramine/dextromethorphan/pseudoephedrine combination), Theraflu (acetaminophen/pseudoephedrine/chlorpheniramine combination), and Norplant.

The fourth fatal case was a 46-year-old male with a history of idiopathic seizure disorder since his teenage years, who died during a seizure episode. He had been treated with Tegretol (carbamazepine) and Neurontin (gabapentin). Advil and Contact (acetaminophen/pseudoephedrine/diphenhydramine combination) were listed as concomitant medication.

The fifth fatal case was a 69-year-old male patient who died of GI hemorrhage following the ingestion of unknown dosage of Advil and Alka-Seltzer (a combination of acetaminophen/pseudoephedrine/chlorpheniramine). The cause of death was considered most likely associated with ibuprofen toxicity.

The sixth fatal case was a 74-year-old female took unknown dosage of Theraflu (acetaminophen/pseudoephedrine/chlorpheniramine) and developed maculopapular rash. The sequential events leading to death were not provided.

In none of the fatal cases the following information was given to allow the adequate assessment of the causal effects of the three ingredients on the events: the level and duration of exposure to the three active ingredients and the relationship between the exposure and time sequence of the events leading to death. Based on the limited information on the cases given the causes of deaths were probably Zonegran induced multi-system organ failure in the first case, hepatic failure due to acetaminophen overdose in the second case, sepsis in the third case, seizure in the fourth case, ibuprofen-related GI hemorrhage in the fifth case, and could not be determined for the sixth case.

Most of the other serious cases followed the same pattern that there were no details to allow assessment of the association between the three ingredients and the events leading to the serious outcomes. In most of the serious cases, except two cases, the concurrent use of the 3 ingredients was not considered as the primary or secondary suspect leading to the serious outcomes based on the initial assessment at the of data collection, but listed among the concurrent medication.

Of the 2 serious cases in which the 3 active ingredients were listed as suspected drugs one was the death of a 69-year-old due to ibuprofen induced GI hemorrhage already discussed above. The second case was a 7-year-old female with a history of reactive airway disorder and allergy to wheat and milk, who developed an episode of hyperventilation, dyspnea, and hyperkinesia 20 minutes after a single dose of Motrin Chewable (ibuprofen) 200mg and Codimal-LA (extended-release of chlorpheniramine 8mg and pseudoephedrine 120mg). She was treated with cromolyn nebulizer and then I.V. Valium and hospitalized. She had similar reactive symptoms 3 minutes after another dose of ibuprofen (Motrin suspension 100mg) received one day after the initial episode. The second episode responded to the treatment with Valium and Solu-Medrol. After being discharged home she experienced another episode 13 hours after the second dose of ibuprofen. The last episode responded to treatment with Prelone. The medication most likely to be the cause of these events was ibuprofen because of the recurrence of the symptoms upon re-challenge (unintentional) with ibuprofen.

An interesting observation was the trend in these serious cases with the concurrent use of multiple OTC cold/flu products (single-ingredient and/or combination products) that contained same or similar ingredients, a potential for the risk of unintentional overdose.

Table 12. Serious cases on the concurrent use of the three active ingredients

Database	*Age Gender*	*Suspected medication*	*Other medication*	*Adverse events*	*Outcome*
FDA SRS	7 female	Codimal-La, Motrin Children's Motrin		Dyspnea, hyperkinesia Hyperventilation, hypotension	Hospitalized
FDA AERS	9 female	Zonegran (PS) Depakene (SS)	Zantac, Xopenex Valium, phenobarbitol Tranxene, Tobramycin Suppositoires A La Glycerine "Gifrer" Motrin, Senokot Scopolamine, Sodium Chloride Advil, Pediacare Cough-Cold Vitamin E, Multi-Vitamins Lacri-Lube, Mineral Oil Emulsion Dimetane, Ceftazidime Sodium Bisco-Lax, Calcium Carbonate Azithromax, Augmentin Paediatric	Alanine aminotransferase increased Aspartate aminotransferase increased Disseminated intravascular coagulation Respiratory failure (exc neonatal) Multi-organ failure, sepsis nos	Death Hospitalized
FDA AERS	14 male	Imitrex	Sinutab Paracetamol Ibuprofen	Abdominal pain upper, nausea Coronary artery spasm, dyspnoea nos Pulsus bigeminus, chest pain supraventricular tachycardia, malaise, vomiting nos Sweating increased, pyrexia Tricuspid valve incompetence Ventricular extrasystoles, Ventricular tachycardia, weakness	Hospitalized
FDA SRS	19 male	Tylenol Nyquil	Advil, Comtrex Aspirin	Dehydration, liver necrosis Myocarditis, overdose	Death
FDA AERS	19 female	Norplant System	Sudafed, Robitussin Dm Nyquil, Maalox Ibuprofen, Deconamine Sr Ceftin	Abdominal pain nos, ectopic pregnancy Intermenstrual bleeding, Menstruation irregular, hemoperitoneum Urination abnormal nos	Hospitalized
Sponsor	21 female	Amoxicillin trihydrate	Hexapneumine, bristamox ibuprofen/pseudoephedrine	Pruritus nos Rash macular	Hospitalized
FDA SRS	22 female	Seldane-D	Naldecon, Albuterol Ibuprofen	Coma, respiratory disorder Vomiting	Hospitalized
FDA SRS	22 female	Advil	Alka-Seltzer Contac	Abdominal pain Gastroenteritis	Hospitalized
FDA AERS	34 female	Nicorette	Tylenol Allergy Sinus (Apap/Chlor-Mal/ Pseudoephedrine) Premarin, Pannaz (Ppa HCl/Chlor-Mal/Scopolamine) Depo-Provera, Advil	Abdominal pain nos, agitation Biliary tract disorder nos Liver function tests nos abnormal Abnormal endoscopic retrograde cholangiopancreatography	Hospitalized
FDA AERS	36 male	Zyprexa (Olanzapine)	Eskalith, Ibuprofen Pseudoephedrine HCl Chlorpheniramine, Prozac	Accident nos Acute abdomen Injury nos	Life threatening Req. Intervent Hospitalized
FDA AERS	38 male	Relenza	Paracetamol Ibuprofen Dimetapp Extentabs Comtrex	Bronchospasm nos, tachycardia nos Dyspnea nos, drug hypersensitivity Hypotension nos, convulsions nos	Hospitalized Require Intervention Life

Database	*Age Gender*	*Suspected medication*	*Other medication*	*Adverse events*	*Outcome*
			Benzonatate Aspirin	Urticaria nos Tachypnea, respiratory rate increased Dermatitis nos, hypersensitivity nos	Threatening
FDA SRS	41 male	Ibuprofen	Alka-Seltzer Plus Maalox	Dizziness, postural hypotension, melena, rectal hemorrhage	Hospitalized
FDA SRS	46 male	Neurontin	Tegretol, Contac Advil	Convulsion Heart Arrest	Death
FDA SRS	48 male	Advil	Contac	Syncope Ulcer Stomach Hem	Hospitalized
Sponsor	52 female	Venlafaxine HCl	Clemastine, Tylenol, Advil, Sinutab, temazepam, clonazepam, chloral hydrate	Operation nos Breast neoplasm nos	Hospitalized cancer
FDA AERS	53 male	Lamivudine 150mg (PS) Zidovudine 30 (SS) Vitamin B Complex/Vitamin C (SS)	Ritonavir, Triamcinolone Acetonide Saquinavir, Trazodone HCl, Lamivudine, Sulfamethoxazole. Simethicone, Trimethoprim, Nutrition Supl, Lisinopril Povidone Iodine, Methocarbamol, Ensure/Vanilla pwd, Guaifenesin DM Pseudoephedrine HCl, Ibuprofen Loperamide HCl, Acetaminophen Ipratropium Bromide, Albuterol Hemorrhoidal HC, Chlorpheniramine HCTZ 50/Triamterene, Fluconazole Folic Acid, Ferrous Sulfate Tab Maleate W/Phenylephrine Hydrochloride Syrup	Pancytopenia	Hospitalized Require Intervention
FDA SRS	61 male	Prozac	Advil, Chlor-trimeton Sudafed, Folic Acid	Abdominal pain, diarrhea Melena, ulcerative colitis	Hospitalized
FDA SRS	63 male	Cardene	Quinamm, Nitroglycerin, Ibuprofen, Alka-Seltzer Plus	Acute myelogenous leukemia Liver Failure, Liver Necrosis Thrombocytopenia	Hospitalized
FDA SRS	69 male	Advil Alka-Seltzer Plus		Gastritis, hematemesis, Melena, weight decrease	Death
FDA AERS	69 female	Evista (Raloxifene HCl)	Vitamin D, Calcium Tylenol Allergy Sinus Ibuprofen	Uterine atony	Hospitalized
FDA SRS	74 female	Theraflu	Librium Motrin	Maculopapular rash	Death
Sponsor	UK	Ibuprofen	Robitussin DM, Nyquil Levonorgestrel, Maalox Deconamine SR, ceftin	Migration of implant, ectopic pregnancy, Haemoperitoneum, dysmenorrhea, Menometrorrhagia, Complication of device removal	Hospitalized
FDA AERS	Female	Clozapine (PS) Quetiapine (SS)	Theraflu Nyquil Norplant Insertion Ibuprofen	Acute circulatory failure, neutropenia Pneumonia nos, sepsis nos, Oxygen saturation decreased White blood cell count decreased	Death

7.7. Drug Abuse and Overdose Experience

Ibuprofen and pseudoephedrine when being used alone, together, or in a combination, had not been shown as having a high potential for drug abuse or overdose based on data presented in Dr. Andrea Leonard-Segal's review (refer to the clinical review of NDA 21-374 dated April 26, 2002 for detail). Chlorpheniramine had not been reported as having a high potential for drug abuse or overdose based on the review of the literature. The abuse and overdose potential for the triple combination could not be adequately assessed because of very limited post-marketing data on the concurrent use of the three active ingredients. Nevertheless, seven overdose cases were identified in the 3 post-marketing databases and summarized in table 13 below.

Only one of the seven cases had a serious outcome, the death of a 19-year-old due to acetaminophen overdose as discussed above in the section 7.6.2. Four cases were accidental overdose in 2-year-old children and were basically asymptomatic. There was one case of intentional overdose in a 22-year-old female psychiatric patient, who took 2 tablets of Alprazolam, 2 tablets of Tylenol #3, and 8 tablets of Sinutab (acetaminophen/pseudoephedrine/chlorpheniramine combination), all at once (on top of her routine medication) in a suicide attempt. Adverse events were not reported and the patient was reported as not suicidal at the follow-up visit. The last case was chronic overdose of ibuprofen by a 24-year-old male who took 2400 to 7200mg of ibuprofen contained in several OTC products daily for 2 months and other OTC products containing pseudoephedrine and chlorpheniramine at unknown dosage. No adverse events were reported in this case.

Table 13. Overdose cases on the concurrent use of the three active ingredients

Database	*Age/sex*	*Suspected medication*	*Other medication*	*Adverse events*	*Outcome*
Sponsor	2 male	Dayquil Sinus Pressure and Pain Relief with Ibuprofen 2 capsules; p.o. one dose	Triaminic unknown dose and duration taking 4 hours earlier	Asymptomatic	(Lost to follow-up)
Sponsor	2 female	Children's Advil Suspension up to 3 tsp p.o. one dose	Pediacare unknown dose and duration	Asymptomatic	None
Sponsor	2 male	Children's Advil Suspension 15mL p.o. one dose	Night-Time Triaminic 1 tsp p.o. one dose	Agitation during sleep	(Lost to follow-up)
Sponsor	2.5 female	Children's Advil Suspension 1 oz p.o. one dose	Pediacare unknown dose and duration	Asymptomatic	None
FDA SRS	19 male	Tylenol and Nyquil of unknown dosage	Advil, Comtrex, and Aspirin of unknown dosage	Liver necrosis and myocarditis consistent with acetaminophen overdose	Death
FDA SRS	22 female	Alprazolam 2 tablets, Sinutab 8 tablets, and Tylenol #3 2 tablets in a suicide attempt	Alprazolam 6mg/day; Nuprin prn, unknown dosage; Sinutab 6 tabs/day for 3 days; Chlor-Trimeton 4-6 tabs day for 2 days	Intentional overdose of multiple drugs in a psychiatric patient; no symptoms reported	None
FDA SRS	24 male	Multiple ibuprofen containing products 2400 to 7200mg/day for 2 months	Ibuprofen Advil Sudafed Coricidin Drixoral	Ibuprofen overdose	None

7.8. Adequacy of Safety Testing

The safety profiles of the three individual ingredients: ibuprofen, pseudoephedrine, and chlorpheniramine, have been well established. Various ibuprofen-containing products of different formulations at both prescription and OTC dose levels had been evaluated in multiple NDAs over the years. Pseudoephedrine, and chlorpheniramine were generally recognized as safe and effective for OTC use with dosing up to 240 mg/day and 24 mg/day, respectively, for adults and children over 12 years, per 21 CFR 341.80(d)(1)(ii) and 341.72(d)(3). Various combination products containing pseudoephedrine, chlorpheniramine, or both active ingredients were also submitted for NDA review and approved in the past years. The potential for drug-drug interactions between the three active ingredients was studied in the single-dose human PK trial (single-dose PK study has been considered the most sensitive in detecting drug-drug interactions as compared to repeated-dose PK study per conversation with Dr. Bashaw). The safety on the repeated use of the triple combination was studied in more than 500 subjects exposed for 7 days. Taking all these factors into consideration: the safety profile of the individual ingredients for OTC use, the lack of interaction between the active ingredients, the frequency and the nature of AEs observed in the clinical study, the adequacy of the safety database was considered acceptable in this particular case.

7.9. Labeling Safety Issues and Post-marketing Commitments

The main labeling safety issues were the addition of the warnings about the potential increase of drowsiness when the product is used with alcohol, sedatives, and tranquilizer and stop using the drug when symptoms continue or get worse. The labeling revision including the reviewer's comments were written by the reviewers Michael Benson (primary reviewer) and Marina Chang (secondary reviewer) in the Division of OTC Drug Products and will not be repeated here (refer to labeling reviews dated October 2, November 7, and December 3, 2002). The final version of the labeling (a copy is attached in the section 10.3 of this review) submitted by the Sponsor on November 25 has included reasonably adequate statements regarding the safe use of the product.

In this reviewer's opinion phase IV post-marketing clinical studies are not required.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

Based on the results of clinical study that 2-tablet dosing was not associated with additional benefit but with increased dose-related toxicity, the recommended dosing is one tablet (ibuprofen 200mg/pseudoephedrine 30mg/chlorpheniramine 2mg) every 4 to 6 hours and not to exceed 6 tablets per 24 hours (see section 10.3 for specific labeling statement).

9. USE IN SPECIAL POPULATIONS

9.1. Effects of Gender, Age, Race, or Ethnicity, and the Adequacy of Analysis

9.1.1. Gender

Based on the subgroup analysis of PK data, gender effect was shown in terms of the slightly (borderline) lowered Cmax (the extent of maximum absorption) of ibuprofen in the triple combination in males. Also, food affected the absorption of pseudoephedrine in the triple combination in males as shown by the slightly (borderline) lowered Cmax and AUC (the maximum and total absorption, refer to PK review for detail). These borderline changes on group mean values were not expected to correlate to clinically significant changes.

The Sponsor did not conduct subgroup analysis of gender effect on efficacy. It would be interesting to compare gender effect on efficacy with the findings of the PK studies.

With regard to gender effect on safety, females reported more AEs in general and per treatment group than males (refer to table 7 and section 7.3.1.7 for detail). Males and females had a similar pattern in terms of the doe-related increase in AE reporting.

9.1.2. Age

Age group analysis on PK data and efficacy data would not be practical because of small number of subjects in the age-specific treatment subgroups. Increasing age group size in an efficacy study would lead to a much larger study sample size, which in turn would lead to the detection of highly significant but small treatment differences due to the overpower of the study. Age effect on efficacy might be better evaluated by meta-analysis of several trials.

Subjects younger than 18 years old reported less AEs per treatment arm than the three older age groups (refer to table 8 for detail). Elderly would be expected of having higher risks for drug-related AEs especially in terms of somnolence and dizziness. However, the comparison of the AE reporting between the elderly and non-elderly could not be made since only few elderly subjects were included in the study. More elderly should have been included in the multiple dose trial for adequate safety analysis of age effects on elderly. On the other hand the dosing recommendation for the triple combination is to limit the single dose to one tablet

only, which would help to reduce the risks associated with the use of the drug in the elderly.

9.1.3. Race or Ethnic Origin

The subgroup analysis based on race could not be conducted because there was not sufficient number of subjects of ethnic minorities to provide valuable information. For the same argument as to sample size needed for adequate analysis in conflict with overpower of the study, the effect of race on efficacy might be better evaluated by meta-analysis of several trials. The effect of race on safety would need to be evaluated in a very large safety trial that enrolls sufficient number of subjects from the representative ethnic groups.

9.2. Pediatric Program

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9.3. Data with Respect to Other Special Populations

The precautions on the use of drug in special populations such as patients with renal or hepatic insufficiency or pregnant females are the same as those for the individual ingredients.

10. CONCLUSIONS, RECOMMENDATIONS, AND LABELING

10.1. Conclusions Regarding Safety and Efficacy

The triple combination of ibuprofen 200mg, pseudoephedrine 30mg, and chlorpheniramine 2mg has been demonstrated as efficacious and reasonably safe to be used for the temporary relief of symptoms associated with allergic rhinitis.

The major benefit of this combination product is the demonstration of efficacy at one-tablet dose, which was shown to be equally efficacious to that of 2-tablet dose. The recommendation of one-tablet single dose will reduce the dose-related risks associated with the use of the product since doubling of the dose of triple combination from one tablet to 2 tablets was associated with dose-related increase in toxicity as demonstrated in the clinical trial (AD-99-02). The addition of ibuprofen 200mg provides additional therapeutic benefits (refer to discussion in section 6.2.3.1 for detail) with no noticeable increase in the incidence of adverse events (the total events as well as the individual events) based on the multiple-dose clinical study (AD-99-02) results. The triple combination provides a dosing convenience for the target population with allergy-associated pain (headache and/or facial pain). The most frequently observed adverse events (AEs) after 7 days of continuous exposure in the clinical study, were somnolence, dizziness, dry mouth, dyspepsia, insomnia, and asthenia, which were all common AEs known to be associated with the use of the 3 individual ingredients at the therapeutic dose.

A potential risk, which is applicable to all the fixed-dose drug combinations, is the unnecessary intake of an ingredient when it is no longer in need as its target symptom(s) resolve. Another potential risk is the risk for accidental overdose with the concurrent use of multiple OTC cold/flu products (single-ingredient and/or combination products) that contain the same or similar ingredients.

The benefit/risk ratio for the OTC use of this combination product, ibuprofen 200mg/pseudoephedrine 30mg/chlorpheniramine 2mg, is considered acceptable in this clinical reviewer's opinion based on the review of the NDA submission.

10.2. Recommendations on Approvability

The proposed OTC marketing of the combination product ibuprofen 200mg/pseudoephedrine 30mg/chlorpheniramine 2mg is recommended for approval by this reviewer, for the temporary relief of symptoms associated with hay fever, upper respiratory allergies, and common cold.

10.3. Labeling

This reviewer agrees with the labeling review written by Marina Chang (the team leader at the OTC Division) dated December 3, 2002, that: "The sponsor has made the changes as requested by the Agency and the color mock-up labels are acceptable".

The final version of the labeling is attached below.

2 pages redacted from this section of the approval package consisted of 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/

Christina Fang
12/23/02 12:56:59 PM
MEDICAL OFFICER

James Witter
12/23/02 02:13:33 PM
MEDICAL OFFICER
This review may be superceded by a revision

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12/23/02 02:21:36 PM
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