

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022113Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA resubmission
Application Number(s)	22-113
Priority or Standard	S
Submit Date(s)	June 21, 2011
Received Date(s)	
PDUFA Goal Date	December 21, 2011
Division / Office	DNCE/ ODE IV
Reviewer Name(s)	Linda Hu
Review Completion Date	November 16, 2011
Established Name	Ibuprofen 200 mg/ Phenylephrine HCl 10 mg/ Chlorpheniramine 4 mg
(Proposed) Trade Name	Advil Allergy & Congestion Relief
Therapeutic Class	Analgesic/ decongestant / antihistamine
Applicant	Pfizer Consumer Healthcare (PCH)
Formulation(s)	Tablet
Dosing Regimen	For adults and children >12 years old: take 1 tablet every 4 hours, while symptoms persist. Do not take more than 6 tablets in 24 hours, unless directed by a doctor.
Indication(s)	--Temporarily relieves the following symptoms associated with hay fever or other upper respiratory allergies and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, and fever; --Reduces swelling of nasal passages; --Temporarily restores freer breathing through the nose
Intended Population(s)	adults and children 12 years and older

Template Version: [March 6, 2009](#)

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>7</b>
1.1	Recommendation on Regulatory Action .....	7
1.2	Risk Benefit Assessment.....	7
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	7
1.4	Recommendations for Postmarket Requirements and Commitments .....	7
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>7</b>
2.1	Product Information .....	7
2.2	Tables of Currently Available Treatments for Proposed Indications .....	9
2.3	Availability of Proposed Active Ingredient in the United States .....	10
2.4	Important Safety Issues With Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	10
2.6	Other Relevant Background Information .....	12
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>12</b>
3.1	Submission Quality and Integrity .....	12
3.2	Compliance with Good Clinical Practices .....	12
3.3	Financial Disclosures.....	13
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>13</b>
4.1	Chemistry Manufacturing and Controls .....	13
4.2	Clinical Microbiology.....	13
4.3	Preclinical Pharmacology/Toxicology .....	13
4.4	Clinical Pharmacology .....	14
4.4.2	Pharmacodynamics.....	14
4.4.3	Pharmacokinetics.....	14
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>23</b>
5.1	Tables of Studies/Clinical Trials .....	23
5.2	Review Strategy .....	23
5.3	Discussion of Individual Studies/Clinical Trials.....	23
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>24</b>
	Efficacy Summary.....	24
6.1	Indication .....	24
6.1.1	Methods .....	24
6.1.2	Demographics.....	24
6.1.3	Subject Disposition.....	24
6.1.4	Analysis of Primary Endpoint(s).....	24
6.1.5	Analysis of Secondary Endpoints(s) .....	25
6.1.6	Other Endpoints .....	25

6.1.7	Pediatric Subpopulation .....	25
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ....	27
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	27
6.1.10	Additional Efficacy Issues/Analyses .....	28
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>28</b>
	Safety Summary .....	28
7.1	Methods.....	28
7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	28
7.1.2	Categorization of Adverse Events.....	32
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	33
7.2	Adequacy of Safety Assessments .....	33
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	33
7.2.2	Explorations for Dose Response.....	34
7.2.3	Special Animal and/or In Vitro Testing .....	34
7.2.4	Routine Clinical Testing .....	34
7.2.5	Metabolic, Clearance, and Interaction Workup .....	34
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	34
7.3	Major Safety Results .....	34
7.3.1	Deaths.....	34
7.3.2	Nonfatal Serious Adverse Events .....	35
7.3.3	Dropouts and/or Discontinuations .....	35
7.3.4	Significant Adverse Events .....	35
7.3.5	Submission Specific Primary Safety Concerns .....	35
7.4	Supportive Safety Results .....	35
7.4.1	Common Adverse Events .....	35
7.4.2	Laboratory Findings .....	36
7.4.3	Vital Signs .....	36
7.4.4	Electrocardiograms (ECGs) .....	37
7.4.5	Special Safety Studies/Clinical Trials.....	37
7.4.6	Immunogenicity.....	37
7.5	Other Safety Explorations.....	37
7.5.1	Dose Dependency for Adverse Events .....	37
7.5.2	Time Dependency for Adverse Events.....	37
7.5.3	Drug-Demographic Interactions .....	37
7.5.4	Drug-Disease Interactions.....	37
7.5.5	Drug-Drug Interactions.....	37
7.6	Additional Safety Evaluations .....	37
7.6.1	Human Carcinogenicity .....	38
7.6.2	Human Reproduction and Pregnancy Data.....	38
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	38
7.7	Additional Submissions / Safety Issues .....	38

<b>8</b>	<b>POSTMARKET EXPERIENCE</b> .....	<b>38</b>
<b>9</b>	<b>APPENDICES</b> .....	<b>44</b>
9.1	Literature Review/References .....	44
9.2	Labeling Recommendations .....	59
9.3	Advisory Committee Meeting.....	62

## Table of Tables

Table 1 Examples of Currently Available Treatments for Proposed Indication.....	9
Table 2 AD-08-10 IBU PK Parameters - Mean (SD) [Median], Ratios, and 90% CIs ....	20
Table 3 AD-08-10 PE PK Parameters - Mean (SD) [Median], Ratios, and 90% CIs ....	21
Table 4 AD-08-10 CHLOR PK - Mean (SD) [Median], Ratios, and 90% CIs .....	22
Table 5 Completed Human Studies for IBUPROFEN/PE/CHLOR .....	23
Table 6 Recommended Dosing (adults and children 12 years of age and over) for Ibuprofen, Phenylephrine and Chlorpheniramine as Single Ingredient Products .....	25
Table 7 Approved Dosing (children 2 to 11 years of age) for IBU, PE, and CHLOR .....	26
Table 8 Number (%) of Subjects Reporting AEs .....	29
Table 9 Subjects reporting AEs by SOC and PT versus Treatment and Study (Original and New Study Data).....	30
Table 10 Numbers of Subjects in Clinical Studies .....	33
Table 11. Demographics .....	34
Table 12 Subject Enrollment in Clinical Trials .....	35
Table 13 RR MI in current IBU users versus non-users (van Staa et al. 2008) .....	51
Table 14 Odds ratios for death or hospitalization for HF or MI (Gislason et al. 2009) with IBU use .....	51

## Table of Figures

Figure 1 AD-08-10 Mean Plasma IBU Concentrations (Linear, through 8 hours).....	18
Figure 2 AD-08-10 Mean Plasma PE Concentrations (Linear, through 8 hours).....	19
Figure 3 AD-08-10 Mean Plasma CHLOR Concentrations (Linear, through 8 hours)...	19
Figure 4 Tennessee Medicaid study of NSAID stroke risk (Roumie et al. 2008) .....	49
Figure 5 Risk of death or MI. Hazard ratio with exposure to NSAIDs in healthy population of 1,028,437 people; error bars show 95% CI (Fosbol et al. 2009). Use of IBU at OTC doses is not associated with any elevated risk.....	52
Figure 6 Advil Cold and Congestion Label .....	60

## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

The proposed combination of ibuprofen 200 mg/chlorpheniramine 4 mg/phenylephrine 10 mg (Advil Allergy & Congestion Relief) has an acceptable clinical safety profile and should be approved for OTC marketing. The chemistry assessment is pending.

### **1.2 Risk Benefit Assessment**

Analgesic/decongestant/antihistamine combination products are allowed under the cough/cold combination monograph, but not with ibuprofen as the analgesic, as ibuprofen is not an ingredient allowed under the monograph. While this combination has not previously been marketed, the individual ingredients have been marketed OTC for a significant time and extent as either an NDA single ingredient product (ibuprofen) or as monograph single ingredient products (phenylephrine and chlorpheniramine). The proposed combination of ibuprofen 200 mg/ phenylephrine 10 mg/chlorpheniramine has an acceptable safety profile for OTC marketing.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Usual post marketing monitoring.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

NA

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Ibuprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID). Like other NSAIDs, it has analgesic, antipyretic, and anti-inflammatory properties. Ibuprofen was first approved for prescription use in 1969 and for OTC use in the UK and US in 1983 and 1984, respectively. Since then, it has become widely used for the temporary relief of acute pain and fever. Pfizer, formerly Wyeth Consumer Healthcare (WCH) markets Advil, a brand of Ibuprofen in the US. The chemical structure is shown below:

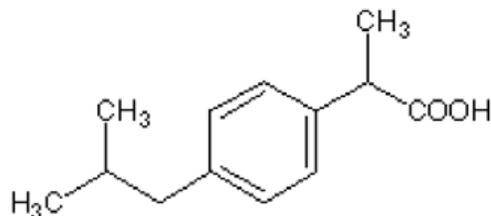
## Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

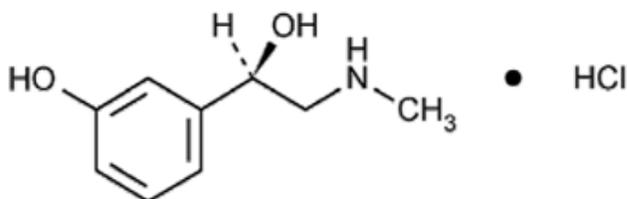
---



Molecular Formula:  $C_{13}H_{18}O_2$

Molecular Weight: 206.28

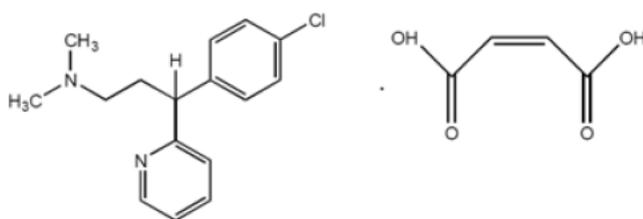
Phenylephrine is a sympathomimetic amine that has been available for use as an OTC nasal decongestant since the early 1960s. PE acts predominantly by a direct effect on alpha-adrenergic receptors. In therapeutic doses, the drug has no substantial stimulant effect on the beta1-adrenergic receptors of the heart and does not stimulate beta2-adrenergic receptors of the bronchi or peripheral blood vessels. It is included as a Category I (safe and effective) oral nasal decongestant in the Final Monograph of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (21 CFR 341.20). The chemical structure is shown below:



Molecular Formula:  $C_9H_{13}NO_2 \cdot HCl$

Molecular Weight: 203.67

Chlorpheniramine, a classical H<sub>1</sub>-receptor antagonist (antihistamine), has been available for more than 40 years as a nonprescription medication for relief of allergic rhinitis symptoms, and is included as a Category I (safe and effective) antihistamine in the Final Monograph of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (21 CFR 341.12). It has been shown to be effective against major histamine-mediated symptoms, i.e., sneezing, itching and rhinorrhea. The chemical structure is shown below:



Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Molecular Weight: 390.86

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Single ingredient pain relievers containing ibuprofen, single ingredient antihistamines containing chlorpheniramine, and single ingredient decongestants containing phenylephrine are readily available and can be combined to treat the indications or relieve the symptoms covered by the Advil Allergy & Congestion Relief product. A combination product with the same ingredients as Advil Allergy & Congestion Relief is not currently available. However, combinations containing a pain reliever, an antihistamine, and a decongestant are available. Examples of available products are listed in Table 1.

Table 1 Examples of Currently Available Treatments for Proposed Indication

Generic Name	Class	Products	Status
Ibuprofen	Analgesic / antipyretic	many	Prescription and OTC
Acetaminophen	Analgesic / antipyretic	many	Prescription and OTC
Loratadine	Antihistamine	many	OTC
Fexofenadine	Antihistamine	many	Prescription and OTC
Chlorpheniramine	Antihistamine	many	Prescription and OTC
Diphenhydramine	Antihistamine	many	Prescription and OTC
Phenylephrine	Decongestant	many	Prescription and OTC
Pseudoephedrine	Decongestant	many	Prescription and OTC

### **2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredients ibuprofen, chlorpheniramine, and phenylephrine are readily available in the United States.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Use of ibuprofen at higher than recommended OTC doses, or for longer than recommended, leads to increased risk of GI bleeds. In addition, cardiovascular risks of NSAIDs have also become a concern. In February, 2005, the European Medicines Agency imposed strengthened warnings on coxibs, stating that they should not be used in patients with coronary heart disease or who have had a stroke, and that they should be used with caution in patients at risk for heart disease. The FDA announced changes in NSAID marketing on April 7, 2005, whereby a black box warning was thereafter required for celecoxib, and strengthened warnings were required for all NSAIDs (including nonselective NSAIDs) to highlight increased risks for cardiovascular events as well as gastrointestinal bleeding. The agency also determined that short-term use of NSAIDs to relieve acute pain, particularly at low doses, did not appear to confer an increased risk of serious adverse CV events. The agency believes the overall benefit versus risk profile for the non-prescription NSAIDs remains favorable when they are used according to the labeled directions. To further encourage the safe use of the non-prescription NSAIDs, the agency requested revisions to product labeling to include more specific information about the potential CV and GI risks, stronger reminders about limiting dose and duration of treatment and a warning for potential skin reactions.

Phenylephrine is a sympathomimetic and is listed as a decongestant in the Final Monograph of cold, cough, allergy, bronchodilator, and antiasthmatic drug products. All drug products containing the sympathomimetic drug, pseudoephedrine, were moved behind the counter in compliance with The Combat Methamphetamine Epidemic Act of 2005 because of diversion to illicit drug manufacturing. Phenylpropanolamine, another drug with sympathomimetic activity, was removed from the market because of an association with intra-cerebral hemorrhages when the drug was used as an appetite suppressant.

Chlorpheniramine is a first generation antihistamine which may be associated with sedation.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

Advil Allergy Sinus caplets, a combination of ibuprofen (IBU) with pseudoephedrine hydrochloride (PSE) and chlorpheniramine maleate (CHLOR), was approved OTC in 2002 (NDA 21-441). This combination PSE product is being reformulated with the substitution of phenylephrine hydrochloride (PE) for pseudoephedrine, because the

PSE-containing product was moved behind-the-counter in compliance with legislation restricting the sale of all pseudoephedrine-containing drug products (The Combat Methamphetamine Epidemic Act of 2005).

Pfizer Consumer Healthcare (PCH) intends to offer IBU/PE/CHLOR 200/10/4 mg tablets, under the name Advil Allergy & Congestion Relief, as an OTC alternative to the PSE-containing combination approved under NDA 21-441.

Pfizer submitted NDA 22-113 on September 25, 2007 and received a Not Approvable Letter (NAL) issued on July 25, 2008. The deficiencies in the NA letter are summarized as:

1. The submitted PK data for phenylephrine are not reliable due to major flaws in the analytical assay methodology. The extrapolation from Study AD-06-06 to Study AQ-05-05 of results of reanalysis of a subset of subject samples, that were analyzed using the flawed original method, is not justified.

A cross-study comparison of ibuprofen PK data from the proposed triple combination caplet (Study AD-05-05) to the historical ibuprofen PK data suggested that the mean Tmax values of ibuprofen increased approximately 1 hr in the presence of phenylephrine and chlorpheniramine. Further analysis is needed to assess the potential impact of delayed Tmax of IBU from the proposed product on clinical efficacy.

The Sponsor was asked to submit pharmacokinetic data for phenylephrine using an adequately validated analytical assay method for unmetabolized (free) phenylephrine in the plasma samples. It was recommended that a repeat BE study should include the to-be-marketed formulation and include an ibuprofen (single ingredient) comparison.

2. The indication for this product, treatment of allergy symptoms, is such that chronic use is likely to occur. Therefore, a qualifying study of 90 days is needed as specified by the ICH Q3B given the potential for a chronic use. The study should use sufficiently high levels of the degradant (b) (4) that can be analytically confirmed.
3. In addition, the following labeling comments were relayed: a. The label should convey a 7-day limit for duration of use (b) (4) in keeping with the monograph dosing for phenylephrine. Labeling should be changed under the "Warnings" and "Directions" sections. b. Under the subsection "Ask a doctor before use if you have", include the term "asthma." c. Under the "Do not use" subsection of Warnings, add the bulleted statement "in children under 12 years of age". In addition, under Directions, change the statement (b) (4) to read "children under 12 years of age: do not use".

4. One of the facilities involved in the submission was deemed not to comply with cGMP requirements. Satisfactory resolution of any deficiencies of the facility was required to assure identity, strength, purity and quality of the drug product.

## 2.6 Other Relevant Background Information

### Citizen's Petition: Pediatric Use of Cold/Cough Drugs

An Advisory Committee meeting was held on October 18 and 19, 2007 to discuss the use of cough and cold drugs (including phenylephrine) in pediatric age groups (0 to 6 years) in response to a Citizen Petition. The Committee recommended that cough and cold products should not be used below 2 years of age either as single ingredients or in combination. The Committee recommended assessing the clinical safety and efficacy of ingredients used in cough and cold products, including pharmacokinetic studies in the 2 to 6 year age group. The Committee did not address use of cough and cold products in the 6 to 12 year age group. Since then, most of the manufacturers have voluntarily relabeled their OTC pediatric drug products to recommend not to use below 4 years of age, even though the Final Monograph allowing dosing down to 2 years has not been changed. The Agency has since determined that studies to address the clinical safety and efficacy of ingredients should also be conducted in the 6 to less than 12 year old age group

### Citizen's Petition: Efficacy of Phenylephrine

A Citizen's Petition was submitted, questioning the efficacy of 10 mg phenylephrine as a decongestant and recommending higher doses. This issue was discussed in the Nonprescription Drug Advisory Committee (NDAC) meeting in December, 2007. The NDAC recommended that the 10 mg phenylephrine dose should remain on the market, given evidence of efficacy for the 10 mg dose, but also recommended efficacy in subpopulations be examined and that higher doses be studied.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Clinical pharmacology has requested a DSI inspection for the PK trial AD-08-10. The inspection is still pending at the time of this review. During the previous review cycle, the PK data for phenylephrine were found to be unreliable due to major flaws in the analytical assay methodology.

### 3.2 Compliance with Good Clinical Practices

No issues have been identified.

### **3.3 Financial Disclosures**

The sponsor submitted Form 3454 certifying that the investigators lacked any significant financial interest in this product or significant equity in the Sponsor.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The 7/25/08 NA letter for NDA 22-113 stated that one of the facilities involved in the submission is deemed not to comply with cGMP requirements. Satisfactory resolution of any deficiencies of the facility is required to assure identity, strength, purity and quality of the drug product. The inspection report is pending. See CMC review for details.

### **4.2 Clinical Microbiology**

NA

### **4.3 Preclinical Pharmacology/Toxicology**

In the last review cycle, three phenylephrine degradants were identified during the stability study. According to the Sponsor, other degradants and impurities will not reach ICH qualification limits during the proposed expiration period.

(b) (4)



## Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

(b) (4)

In response, Pfizer submitted the non-clinical Study No.7G31.BTL: A Repeated Dose Ninety Day Oral Toxicity Study in Sprague-Dawley Rats. The Pharmtox reviewer Dr. Harrouk found that the study had adequate exposure to the drug combination and to the (b) (4) impurity and did not indicate a chronic toxicity risk at up to (b) (4) in this combination. See Pharm Tox review for details.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

See 2.1

#### 4.4.2 Pharmacodynamics

No new pharmacodynamic data were submitted with this application.

#### 4.4.3 Pharmacokinetics

Pfizer conducted study **AD-05-05** to support the initial submission of NDA 22-113. AD-05-05 was a 3-arm, single dose, PK study performed by one investigator at a single site, comparing: IBU/PE/CHLOR 200/10/4 mg caplet – fasted; IBU/PE/CHLOR 200/10/4 mg caplet – fed; and Motrin IB (IBUPROFEN 200 mg/tablet), Sudafed PE (PE 10 mg/tablet), and Chlor-Trimeton Allergy (CHLOR 4 mg/tablet) single ingredient products administered concomitantly in the fasted state. Forty-one subjects were enrolled (19 males and 22 females) with forty subjects completing all three treatment periods. Under fasted versus fed conditions, the rate and extent of absorption were equivalent for the active ingredients IBU and CHLOR, but Tmax for PE was delayed in the presence of food. Furthermore, under fasted conditions, the rate and extent of absorption of IBU, PE, and CHLOR absorption from IBU/PE/CHLOR caplets was equivalent relative to single entity IBU, PE, and CHLOR administered concurrently. A cross-study comparison of ibuprofen PK data from the proposed triple combination caplet (Study AD-05-05) to the historical ibuprofen PK data suggested that the mean Tmax values of ibuprofen increased approximately 1 hr in the presence of phenylephrine and chlorpheniramine.

After completing study AD-05-05, Pfizer changed the final to-be-marketed formulation so as to include an antioxidant preservative (b) (4) propyl gallate or "PG" (b) (4), below the ICH threshold level of

## Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

(b) (4). Propyl gallate is a GRAS ingredient, listed under “substances added directly to human food” per 21 CFR 184.1660.

Accordingly, PCH then conducted PK study **AD-06-06**, a study that compared the IBU/PE/CHLOR formula studied in AD-05-05 with the IBU/PE/CHLOR formulation intended for commercialization containing (b) (4) PG. This was a two-way crossover bioequivalence study at single site, with one investigator. Forty-two subjects (27 male and 15 female) were enrolled, and 40 subjects completed the study. In study AD-06-06, the two products were bioequivalent for IBU with a T<sub>max</sub> of 1.95 and 1.69 hours, for the non-PG and PG formulations, respectively. Similarly, the two products were bioequivalent for CHLOR on AUC and C<sub>max</sub>, with comparable T<sub>max</sub> values. The pharmacokinetic trials AD-06-06 or AD-05-05 whose results were used to demonstrate bioequivalence to single ingredient PE, were found to have employed a flawed methodology. A new PE assay, which measures free PE, was developed and validated, and it was used in study AD-08-10.

In the complete response to the 7/25/08 NA letter, Pfizer submitted **Study AD-08-10**, using the final to-be-marketed formulation. This PK study employed the revised and validated assay that measures free PE in the sample, as opposed to the total PE (free PE + conjugated PE) assay that was used in studies AD-05-05 and AD-06-06. This study investigated ibuprofen drug interaction, formulation effects and foods effects.

**Study AD-08-10** characterized the rate and extent of IBU, PE and CHLOR absorption under fasted conditions from IBU/PE/CHLOR 200/10/4 mg caplets compared to marketed Motrin IB (IBU 200 mg), Sudafed PE (PE 10 mg) and Chlor-Trimeton (CHLOR 4mg) single entity products, administered concomitantly, and to Motrin IB (IBU 200 mg) administered alone. The study also compared the rates and extents of IBU, PE and CHLOR absorption from the IBU/PE/CHLOR combination under fasted and fed conditions.

Under fasted conditions, the IBU/PE/CHLOR caplet was bioequivalent in AUC and in C<sub>max</sub> for IBU to the three single ingredients administered concomitantly. The mean IBU T<sub>max</sub> for the IBU/PE/CHLOR caplet was 34 minutes later than that for Motrin IB + Sudafed PE + Chlor-Trimeton. The IBU/PE/CHLOR caplet was also bioequivalent to Motrin alone for both AUC and C<sub>max</sub>. The IBU T<sub>max</sub> for the combination was longer by 31 minutes compared to Motrin tablets alone.

With regard to PE under fasted conditions, the IBU/PE/CHLOR caplet was bioequivalent for AUC to the three single ingredients administered concomitantly. For C<sub>max</sub>, the mean C<sub>max</sub> ratio was 90.4%, but the lower bound of the 90% confidence interval for PE C<sub>max</sub> was 79.7%. The statistical model used in the analysis included the data from all PE-containing treatment groups, including the IBU/PE/CHLOR fed treatment arm. When the fed treatment arm is not included in the analysis, the 90% confidence interval for bioequivalence was satisfied (81.0, 100.9).

*MO Comment. The Cmax for PE just falls outside the CI for bioequivalence, but this small difference is not clinically meaningful and is acceptable.*

Regarding CHLOR under fasted conditions, the IBU/PE/CHLOR caplet was bioequivalent (AUC and Cmax) to the three single ingredients administered concomitantly. Under fed versus fasted conditions, the IBU/PE/CHLOR caplet was bioequivalent (AUC and Cmax) to CHLOR. Both IBU and PE were bioequivalent for AUC under fasted versus fed conditions. A food effect was observed for Cmax with IBU and PE.

*MO Comment. There is a food effect for Cmax with IBU and PE which does not warrant a label change according to the biopharm assessment. See clinical pharmacology review for further discussion.*

Pfizer notes that other OTC-approved IBU products, with a PK profile similar to that of IBU/PE/CHLOR, have been found to provide adequate analgesia (defined as onset of analgesia within one hour) or fever reduction. The Sponsor has provided four examples that consist of IBU products with Tmax ranging between 110-131 minutes (the mean Tmax of IBU/PE/CHLOR was 138 minutes). The four products have been shown to be effective within one to two hours by different measures including pain intensity difference scores, fever reduction, sleep latency (a known surrogate of pain relief) and the proportion of subjects requiring rescue medication within 1-2 hours after dosing. The four products cited are:

**Advil Allergy Sinus, NDA 21-441 (IBU/PSE/CHLOR)**  
**Advil Chew Tabs, NDA 20-944 (IBU)**  
**Motrin Chew Tab, NDA 20-135 (IBU)**  
**Advil PM Caplets, NDA 21-394 (IBU and diphenhydramine)**

*MO Comment. According to the PK reviewer, the historical data from these NDAs provide adequate evidence to conclude that prolongation of Tmax would not have significant impact on the IBU-dependent efficacy of the triple combination product of IBU/PE/CHLOR. Based on a Sponsor-developed a PK/PD model for IBU in dental pain, the PK reviewer stated that the time difference between Motrin IB and IBU/PE/CHLOR to first perceptible pain relief in study AD-08-10 is likely to be less than 6 minutes. The median Tmax for Motrin IB was 90.5 min and that for IBU/PE/CHLOR was 120 min. See also review by Dr. Shibuya (2010, NDA 22-565).*

Additional details follow on the submitted study AD-08-10.

**Study AD-08-10 Title:** A Four-Way Crossover, Bioavailability Study Of A Caplet Formulation Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 4 mg

**INVESTIGATOR:** Thomas J. Legg, D.O.

## Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

**STUDY CENTERS:** Clinical Site: Bio-Kinetic Clinical Applications, 1816 W. Mount Vernon, Springfield, MO 65802 Analytical Site: PPD Development, 2244 Dabney Road, Richmond, VA 23230

**STUDY PERIOD:** 24 October 2009 – 19 November 2009

### **OBJECTIVES:**

- To characterize under fasted conditions, the rate and extent of absorption of ibuprofen (IBU), phenylephrine (PE) and chlorpheniramine (CHLOR) from a caplet containing IBU/PE/CHLOR 200/10/4 mg compared to Motrin IB (IBU 200 mg), Sudafed PE (PE 10 mg), and Chlor-Trimeton Allergy (CHLOR 4 mg) administered concurrently;
- To characterize the rate and extent of absorption of IBU, PE and CHLOR from a caplet containing IBU/PE/CHLOR 200/10/4 mg administered under fasted conditions compared to a caplet containing IBU/PE/CHLOR 200/10/4 mg administered under fed conditions;
- To characterize, under fasted conditions, the rate and extent of absorption of IBU from a caplet containing IBU/PE/CHLOR 200/10/4 mg compared to Motrin IB (IBU 200 mg) administered alone.

### **STUDY TREATMENTS:**

- Treatment A: one combination caplet containing IBU 200 mg, PE 10 mg and CHLOR 4 mg administered under fasted conditions;
- Treatment B: one combination caplet containing IBU 200 mg, PE 10 mg and CHLOR 4 mg administered under fed conditions;
- [reference therapy] Treatment C: one Motrin IB tablet (IBU 200 mg/tablet), one Sudafed PE tablet (PE 10 mg/tablet) and one Chlor-Trimeton Allergy tablet (CHLOR 4 mg/tablet) administered concurrently under fasted conditions
- Treatment D: one Motrin IB tablet (IBU 200 mg/tablet), administered under fasted conditions

The duration of treatment was a maximum of 72 hours post-dosing for Treatment Periods A, B and C. It was a maximum of 24 hours for Treatment Period D. Each treatment period was separated by a washout interval of 7 days.

Bioequivalence was based on PK data of IBU, unconjugated PE and CHLOR.

Bioequivalence of the PK parameters AUC<sub>0-t</sub>, AUCL, and C<sub>max</sub> was analyzed using two one-sided tests (AUCL and C<sub>max</sub> were considered primary parameters). Specifically, a 90% two-sided confidence interval (CI) was calculated for the relative bioavailability of test versus reference formulation, based on the least square means. Other PK parameters, T<sub>max</sub>, t<sub>1/2</sub>, K<sub>el</sub>, V<sub>d</sub>, and CI are summarized. Bioequivalence was declared if the 90% two-sided CI for the ratio is between 0.8 and 1.25 for log transformed PK parameters.

The study enrolled healthy male/female volunteers between 18-45 years of age with body mass index between 18-29 kg/m<sup>2</sup> and body weight of at least 50 kg. Fifty-six (56) healthy male and female subjects were enrolled to ensure that approximately 48

subjects would complete the study, and all enrolled subjects completed the study. One subject (# 10047) was considered unevaluable for CHLOR in the second treatment period (Treatment C), because he had a pre-dose concentration of CHLOR that was higher than 5% of C<sub>max</sub>. Another subject (#10048) was considered unevaluable for IBU, PE and CHLOR in the third treatment period (Treatment A) in which he received IBU/PE/CHLOR 200/10/4 mg caplet under fed conditions (Treatment B), because he vomited twice within the time window of 2 times the median T<sub>max</sub> of all three active ingredients.

The mean plasma IBU, PE and CHLOR concentration curves including all evaluable subjects are presented below in Figures 1-3. The PK summary results for IBU, PE, and CHLOR for the different comparisons with the primary analysis population are summarized in Table 2, Table 3, and Table 4 which follow.

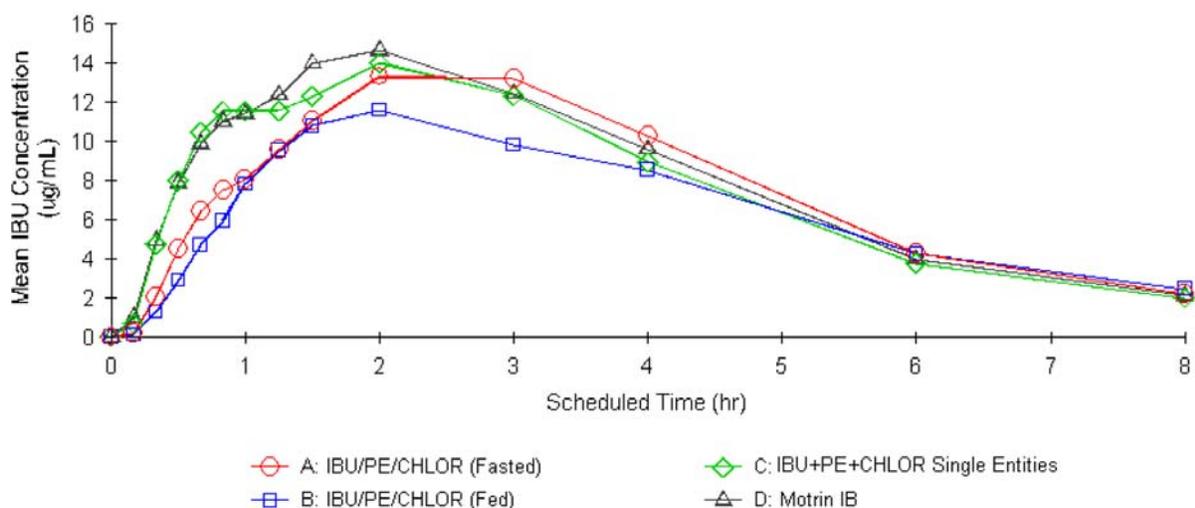


Figure 1 AD-08-10 Mean Plasma IBU Concentrations (Linear, through 8 hours)

Figure 1 shows a higher C<sub>max</sub> and AUC for the combination product under fasted versus fed conditions. Figure 1 also shows a delay in T<sub>max</sub> of 34 minutes for IBU for the combination, under fasted conditions, when compared to the single ingredient formulations, and a delay of 31 minutes when compared to Motrin IB.

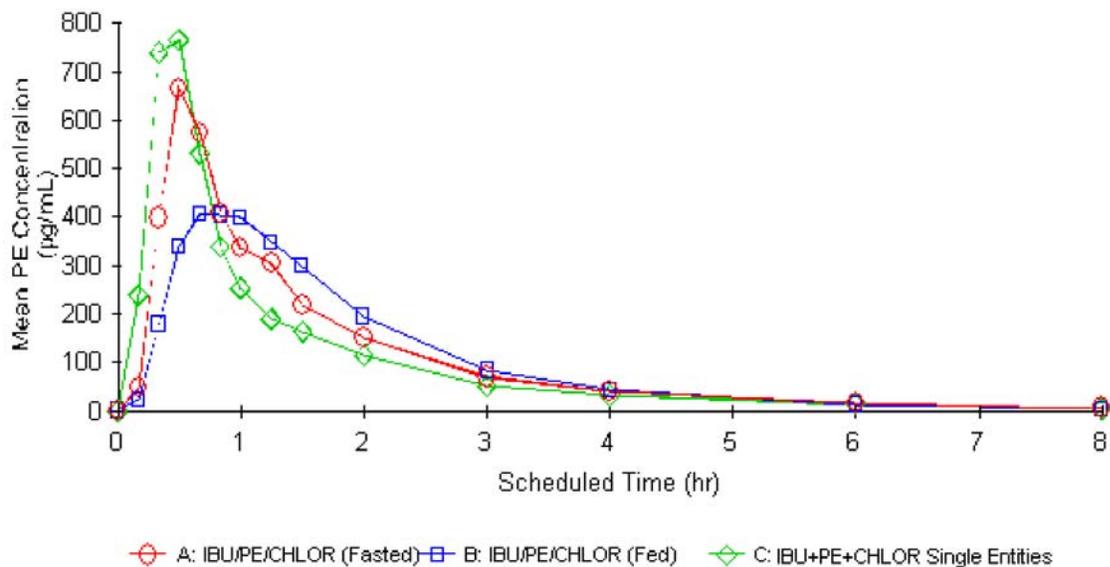


Figure 2 AD-08-10 Mean Plasma PE Concentrations (Linear, through 8 hours)

Figure 2 shows a higher plasma PE C<sub>max</sub> for the single entity products and the combination product under fasted conditions, versus the combination product under fed conditions. Figure 2 also shows similar T<sub>max</sub> values for PE for the combination under either fasted or fed conditions, when compared to the single ingredient formulations.

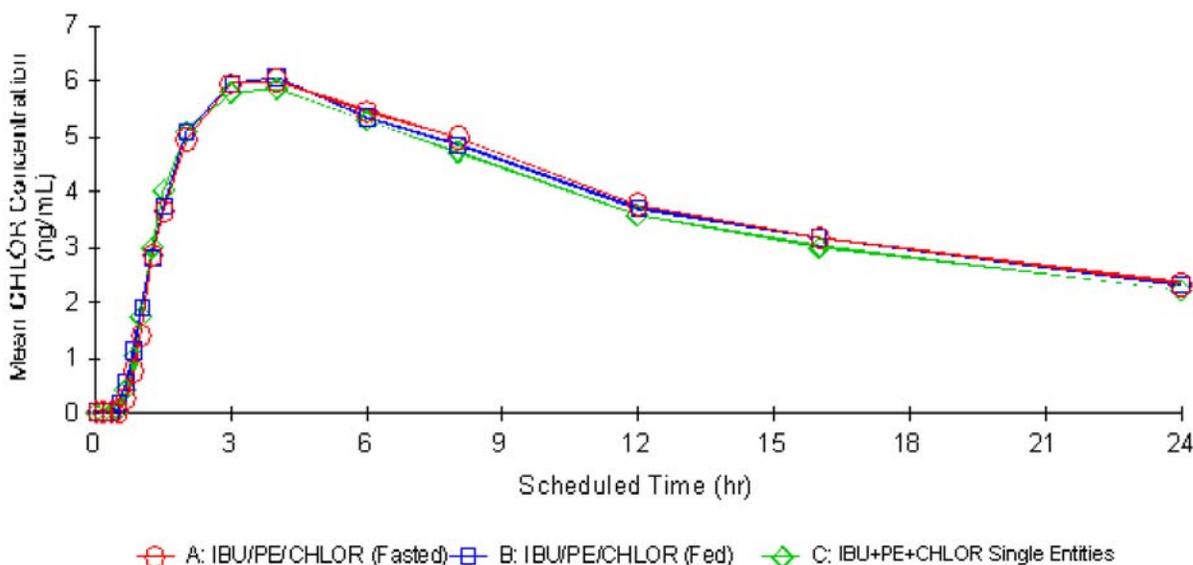


Figure 3 AD-08-10 Mean Plasma CHLOR Concentrations (Linear, through 8 hours)

Figure 3 shows similar plasma concentrations of CHLOR for the combination under either fasted or fed conditions, when compared to the single ingredient formulations.

The PK results for IBU in AD-08-10 are summarized below.

Table 2 AD-08-10 IBU PK Parameters - Mean (SD) [Median], Ratios, and 90% CIs

Treatment	AUCL	AUCI	C <sub>max</sub>	T <sub>max</sub>
	(mcg.hr/mL)	(mcg.hr/mL)	(mcg/mL)	(min)
	Mean (SD) [Median]			
<b>IBU + PE +CHLOR Caplet – fasted (A) (n=56)</b>	67.1 (15.6)	68.4 (15.6)	17.7 (4.3)	137.8 (53.7) [120.0]
<b>IBU + PE +CHLOR Caplet – fed (B) (n=55)</b>	60.6 (13.9)	62.1 (14.1)	14.7 (4.3)	131.5 (73.2) [120.0]
<b>Single Entities – fasted (C) (n=56)</b>	67.3 (16.1)	68.4 (16.2)	19.6 (4.7)	103.8 (57.4) [105.0]
<b>Motrin IB Tablet – fasted (D) (n=56)</b>	70.5 (16.2)	71.8 (16.4)	20.5 (4.6)	107.3 (56.9) [90.5]
Ratio (90% Confidence Intervals)^				
<b>A/C* (%)</b>	100.1 (97.5-102.7)	100.3 (97.7-102.9)	90.7 (85.2-96.6)	—
<b>B/A* (%)</b>	90.1 (87.8-92.5)	90.6 (88.3-93.0)	81.7 (76.7-87.0)	—
<b>A/D* (%)</b>	95.0 (92.6-97.6)	95.3 (92.8-97.8)	86.2 (81.0-91.9)	—

^: Based on fitted log-transformed parameters; \*: Reference formulation

Note: Median is presented to T<sub>max</sub> only.

For IBU, the combination product was BE to the single ingredients taken concomitantly, and to Motrin, under fasted conditions. The combination product under fed conditions, compared to fasted conditions, was lower in AUC but within BE limits; but under fed conditions, the IBU C<sub>max</sub> was reduced below the BE limit (90% CI lower limit ratio at 76.7%) for fed compared to the fasted state.

## Clinical Review

Linda Hu

NDA 22-113

Advil Allergy &amp; Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

Table 3 AD-08-10 PE PK Parameters - Mean (SD) [Median], Ratios, and 90% CIs

Treatment	AUCL (pg.hr/mL)	AUCI (pg.hr/mL)	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (min)
	Mean (SD) [Median]			
<b>IBU + PE +CHLOR Caplet – fasted (A) (n=56)</b>	848.8 (274.9)	892.5 (310.0)	867.4 (456.2)	39.2 (19.3) [30.0]
<b>IBU + PE +CHLOR Caplet – fed (B) (n=55)</b>	817.0 (206.3)	842.0 (207.3)	650.1 (377.3)	59.5 (27.3) [50.0]
<b>Single Entities – fasted (C) (n=56)</b>	803.8 (240.7)	845.9 (249.9)	992.6 (793.2)	28.1 (15.3) [30.0]
<b>Ratio (90% Confidence Intervals)^</b>				
<b>A/C* (%)</b>	104.6 (99.7-109.7)	104.12 (99.0-109.5)	90.4 (79.7-102.5)	—
<b>B/A* (%)</b>	97.8 (93.3-102.7)	96.4 (91.6-101.3)	77.3 (68.2-87.8)	—

^: Based on fitted log-transformed parameters; \*: Reference formulation

Note: Median is presented to T<sub>max</sub> only.

For PE, the combination product was BE to the single ingredients taken concomitantly, under fasted conditions, except for the 90% CI lower limit ratio of C<sub>max</sub> which is very close to the limit for BE (79.7%). However, for the combination product under fed conditions, versus fasted conditions, the C<sub>max</sub> for PE was reduced below the BE limit (68.2% at the lower end of the CI), although the AUC for PE was within the BE limits.

Table 4 AD-08-10 CHLOR PK - Mean (SD) [Median], Ratios, and 90% CIs

Treatment	AUCL	AUCI	C <sub>max</sub>	T <sub>max</sub>
	(ng.hr/mL)	(ng.hr/mL)	(ng/mL)	(min)
	Mean (SD) [Median]			
IBU + PE +CHLOR Caplet – fasted (A) (n=56)	145.8 (57.0)	165.1 (76.1)	6.7 (2.3)	212.4 (90.9) [180.0]
IBU + PE +CHLOR Caplet – fed (B) (n=55)	141.7 (51.1)	160.8 (73.8)	6.8 (1.5)	203.7 (87.5) [180.0]
Single Entities – fasted (C) (n=56)	135.5 (52.0)	153.2 (66.3)	6.4 (2.0)	226.4 (103.6) [240.0]
Ratio (90% Confidence Intervals)^				
A/C* (%)	106.3 (102.9-109.8)	105.8 (102.5-109.2)	103.6 (98.3-109.3)	—
B/A* (%)	99.4 (96.3-102.7)	99.1 (96.0-102.3)	105.0 (99.6-110.8)	—

^: Based on fitted log-transformed parameters; \*: Reference formulation

Note: Median is presented to T<sub>max</sub> only.

For CHLOR, the combination product was bioequivalent under fed versus fasted conditions in terms of both AUC and C<sub>max</sub>. The combination product under fasted conditions was also bioequivalent to the single ingredients taken concomitantly.

### Summary

Under fasted conditions, the IBU/PE/CHLOR caplet was bioequivalent (AUC and C<sub>max</sub>) to single ingredient IBU, PE and CHLOR administered concomitantly for IBU and CHLOR. PE concentrations fell slightly outside the lower bound of the 90% confidence interval on C<sub>max</sub> (79.7%), however this small difference would not be clinically significant. Furthermore, bioequivalence could be declared on C<sub>max</sub> for PE if the fed treatment group was not included in the statistical analysis. The IBU/PE/CHLOR caplet was also bioequivalent to single ingredient Motrin IB for both AUC and C<sub>max</sub>. IBU T<sub>max</sub> for the combination tablet was 34 minutes later than for co-administered IBU+PE+CHLOR and 31 minutes later than Motrin IB. Under fed versus fasted conditions, the IBU/PE/CHLOR caplet was bioequivalent (AUC and C<sub>max</sub>) to CHLOR. A food effect was observed for C<sub>max</sub> with IBU and PE.

*MO Comment.* The Advil Allergy & Congestion Relief triple combination product is essentially bioequivalent to the single ingredients administered concomitantly. There is a food effect with a lower C<sub>max</sub> for both IBU and PE. The T<sub>max</sub> for IBU in this combination product is comparable to that in previously approved IBU-containing products and is acceptable. (Also see Shibuya review 2010, NDA 22-565).

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 5 Completed Human Studies for IBUPROFEN/PE/CHLOR

Study No.	Investigator	Study Design and Duration	Purpose	Treatment/Dose
AD-05-05	Aziz Laurent, MD	72-hour, randomized, inpatient, open label, 3-way crossover, single dose, single center	Drug interaction Formulation effects Food effects	A: IBU/PE/CHLOR 200/10/4 mg fasted B: IBU/PE/CHLOR 200/10/4 mg fed C: Motrin IB (IBU 200 mg tablet) plus Sudafed PE (PE 10 mg tablet) plus Chlor-Trimeton Allergy (CHLOR 4 mg tablet) fasted
AD-06-06	Richard LaRouche, MD	72-hour, randomized, inpatient, open label, 2-way crossover, single dose, single center	Bridge formulations	A: IBU/PE/CHLOR 200/10/4 mg without propyl gallate mg fasted B: IBU/PE/CHLOR 200/10/4 mg with propyl gallate fasted
AD-08-10	Thomas Legg, DO	72-hour, randomized, inpatient, open label, 4-way crossover, single dose, single center	Drug interaction Formulation effects Food effects	A: IBU/PE/CHLOR 200/10/4 mg fasted B: IBU/PE/CHLOR 200/10/4 mg fed C: Motrin IB (IBU 200 mg tablet) + Sudafed PE (PE 10 mg tablet) + Chlor-Trimeton Allergy (CHLOR 4 mg) fasted D: Motrin IB (IBU 200 mg tablet) fasted

### 5.2 Review Strategy

This is a resubmission of NDA 22-113 which includes a safety supplement comprising a literature review, an analysis of spontaneous adverse event data and adverse events reported in clinical trials. One new clinical trial is included in the resubmission, PK trial AQ-08-10.

### 5.3 Discussion of Individual Studies/Clinical Trials

Pfizer submitted a complete response to the NA letter on June 21, 2011 (see section 2.5). The Sponsor provided the new PK study AD-08-10 which investigated ibuprofen drug interaction effects, formulation effects and food effects using the to-be-marketed formulation. Study AD-08-10 used a newly developed and validated analytical method

for free phenylephrine (PE) in plasma. This trial is discussed in section 4.4.3 and the safety sections which follow. This trial is also being reviewed by Dr. Roy.

In addition, Pfizer submitted the non-clinical Study No.7G31.BTL: A Repeated Dose Ninety Day Oral Toxicity Study in Sprague-Dawley Rats. This study was conducted to qualify degradant [REDACTED] (b) (4) at appropriate dose levels. Dr. Harrouk is reviewing this study.

The complete response to the NA letter also includes a Safety Update, a tabular listing of the three human studies involving IBU/PE/CHLOR formulations, and safety data from the three clinical studies supporting the NDA. These are the single-dose, crossover studies AD-05-05, AD-06-06, and AD-08-10 which enrolled a total of 139 subjects. The first two of these were previously submitted to NDA 22-113. This information is discussed below.

## **6 Review of Efficacy**

### **Efficacy Summary**

No efficacy data are provided in this submission. Efficacy studies have been conducted for the IBU/PSE/CHLOR formulation (NDA 21-441) at the time of its approval. The new combination is replacing pseudoephedrine with phenylephrine. No new efficacy studies have been requested by FDA to support this application; to date, no efficacy studies have been conducted on a combination product containing IBU, PE, and CHLOR.

### **6.1 Indication**

NA

#### **6.1.1 Methods**

NA

#### **6.1.2 Demographics**

NA

#### **6.1.3 Subject Disposition**

NA

#### **6.1.4 Analysis of Primary Endpoint(s)**

NA

### 6.1.5 Analysis of Secondary Endpoints(s)

NA

### 6.1.6 Other Endpoints

NA

### 6.1.7 Pediatric Subpopulation

The Sponsor submitted a pediatric plan for Advil Allergy and Congestion Relief, whose individual ingredients are marketed for nonprescription use in children:

- Ibuprofen is approved OTC as an analgesic and antipyretic down to the age of 6 months.
- Phenylephrine is marketed under the final monograph “For the temporary relief of nasal congestion due to the common cold” with dosing down to the age of 2.
- Chlorpheniramine is marketed under the monograph “For the temporary relief of runny nose, sneezing, itching or the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies” down to the age of 6. Professional labeling for chlorpheniramine allows children to be dosed down to the age of 2.

For adults and children 12 years and older (see Table 6), the 3 ingredients IBU, PE and CHLOR can be administered in a combination product at a 4 hour dosing interval, consistent with approved single ingredient dosing directions. However, this is not the case for a combination product containing IBU, PE and CHLOR in the 2 to 11 year old pediatric age group, because recommended dosing intervals are mismatched (see Table 7). For this age range, ibuprofen is dosed every 6-8 hours, whereas CHLOR is dosed every 4-6 hours and PE is dosed every 4 hours.

Table 6 Recommended Dosing (adults and children 12 years of age and over) for Ibuprofen, Phenylephrine and Chlorpheniramine as Single Ingredient Products

	<u>Ibuprofen</u> <sup>1</sup>	<u>Phenylephrine</u> <sup>2</sup>	<u>Chlorpheniramine</u> <sup>3</sup>
Dose (adults and children 12 years of age and over)	200-400 mg	10 mg	4 mg
Dosing Interval	Every 4-6 hours	Every 4 hours	Every 4-6 hours
Maximum Daily Dose	1200 mg	60 mg	24 mg

<sup>1</sup> ADVIL® NDA 18-989    <sup>2</sup> 21 CFR 341.80(d)(1)    <sup>3</sup> 21CFR341.72

Table 7 Approved Dosing (children 2 to 11 years of age) for IBU, PE, and CHLOR

		IBU	PE	CHLOR
Single dose	2 - < 6 yrs	100 mg	2.5 mg	1 mg*
	6 - < 12 yrs	200 mg	5.0 mg	2 mg
Dosing interval		6-8 hrs	4 hrs	4-6 hrs
Maximum daily dose	2 - < 6 yrs	400 mg	15 mg	6 mg*
	6 - < 12 yrs	800 mg	30 mg	12 mg

\* Chlorpheniramine professional labeling

### Children 0 to < 2 years of age:

The Sponsor is requesting a waiver for children aged 0 to < 2 years since FDA has stated that OTC cough and cold medicines in infants and children under age 2 should not be used because serious side effects may occur.

### Children 2 to 11 years of age:

The Sponsor is requesting a deferral for those aged 2 to 11 years. The recommended dosing intervals for the three ingredients IBU, PE and CHLOR do not match in the 2 to 11 year old pediatric population as they do for adults and children 12 years and above.

For children under the age of 12 the Sponsor is proposing labeling that mirrors the language used in the 2 ingredient product Advil Congestion Relief (ibuprofen 200 mg/phenylephrine 10 mg): **Do not use because this product contains too much medication for children under this age.**

The Sponsor has performed PK modeling analyses for NDA 22-565 in order to determine if a common dose and dosing interval can be identified that can provide pediatric exposures comparable to adult exposures for phenylephrine and ibuprofen. The Sponsor was not able to identify a single phenylephrine dose (scaled by age per the OTC monograph) that completely met assumed safety and efficacy constraints when dosed at a 6-hour interval. Instead, the Sponsor proposes higher than monograph allowed PE dosing (b) (4) with a six hour dosing interval. The Sponsor says that these doses are proposed so as to not exceed the serum levels of PE dosed at (b) (4) in adults; however, (b) (4) is not an approved adult dose so safety has not been established. The only approved dose for PE in adults is 10 mg although ongoing drug development programs are exploring higher than 10 mg doses in adults. (b) (4)

The Sponsor is proposing to conduct the following two studies:

STUDY 1- single dose PK study in children between the ages of 6 to less than 12 This will be a 1-arm, single and multiple dose PK study conducted in children 6 to less than 12 years of age with allergic rhinitis.

STUDY 2- single dose PK study in children between the ages of 2 to less than 6 This will be a 1-arm, single and multiple dose PK study conducted in children 2 to less than 6 years of age. The study population will consist of subjects with allergic rhinitis.

**Children 12 to 17 years of age:**

The Sponsor is proposing labeling for those aged 12 to < 17 to be the same as for adults. The Sponsor is referencing the monograph for allowed single and maximum daily doses of PE and CHLOR. The Sponsor states that the currently approved single and maximum daily doses of IBU, PE and CHLOR for adolescents 12-17 years of age are the same as the adult dose. The Sponsor believes that the currently developed product is suitable for use in this population and does not require further study.

MO Comment. These proposals were presented to PeRC, which felt that more information is needed for the single ingredients before studying the combination product, since the proposed dose of PE is above that given in the monograph for the 2 to < 12 year old age group. PeRC requested an amended pediatric plan prior to product approval in the adult population.

*DNCE's recommendations follow.*

- *Grant a waiver for pediatric studies for children ages 0 to < 2 years.*
- *Label the product for children 12 to 17 years the same as for adults since 2 ingredients are found in the monograph, and there is considerable efficacy and safety information for ibuprofen. The label should direct children under 12 years of age not to use the product ("Do not use because this product contains too much medication for children under this age").*
- *Conduct single and multiple dose PK studies, and clinical safety and efficacy trials to evaluate the relief of cold symptoms in children 2 to < 12 years of age. However, efficacy for the relief of allergy symptoms can be extrapolated from adult studies.*

The amended pediatric plan from the Sponsor is pending at the time of this review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

NA

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

NA

#### 6.1.10 Additional Efficacy Issues/Analyses

NA

## 7 Review of Safety

### **Safety Summary**

The original submission of NDA 22-113 for Advil Allergy & Congestion Relief was reviewed in March, 2008 by Dr. Osborne. The safety evaluation for the ibuprofen 200 mg/ phenylephrine 10 mg/ chlorpheniramine 4 mg caplet included a review of the adverse event data from one clinical study (bioequivalence study AD-05-05), the Sponsor's adverse event database, data from the FDA AERS database, and a review of the literature. Dr. Osborne found the product to have an acceptable safety profile. The resubmission of NDA 22-113 includes a safety supplement comprising a literature review, an analysis of spontaneous adverse event data and adverse events reported in clinical trials.

### **7.1 Methods**

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The studies used to evaluate safety are listed in Table 5 in Section 5.1.

The details of adverse events from study AD-05-05 were submitted in NDA 22-113 and reviewed previously. Safety data from AD-06-06 and AD-08-10 were included in this submission. This review will analyze safety data from all three studies. All AEs that occurred during these three studies are summarized by MedDRA System Organ Class, and Preferred Term. As seen in the following table, GI Disorders and Nervous System Disorders were the system organ classes with the most number of subjects reporting AEs. These events occurred across studies and across treatments.

Table 8 lists the number and percent of subjects reporting AEs by system organ class, treatment and study. Table 9 lists the number and percent of subjects reporting AEs by system organ class, preferred term, treatment and study.

Table 8 Number (%) of Subjects Reporting AEs

Adverse Events(AEs) (by MedDRA Version 9.0/12.1) SOC and Preferred Term	Original Data			New Safety Data					
	AD0505			AD0606		AD0810			
	Trt A	Trt B	Trt C	Trt A	Trt D	Trt D	Trt E	Trt C	Trt F
N	40	41	40	41	41	56	56	56	56
ANY ADVERSE EVENT: No. of AEs**	7	5	9	12	17	8	12	12	6
No. (%) of Subjects**	7(17.5)	5(12.2)	7(17.5)	9(22.0)	12(29.3)	7(12.5)	5(8.9)	8(14.3)	6(10.7)
Eye disorders	0	0	0	1(2.4)	0	0	0	0	1(1.8)
Gastrointestinal disorders	3(7.5)	1(2.4)	2(5.0)	2(4.9)	1(2.4)	3(5.4)	2(3.6)	2(3.6)	2(3.6)
General disorders, Administration site	0	1(2.4)	0	3(7.3)	3(7.3)	0	1(1.8)	0	0
Infections and infestations	0	0	0	0	0	1(1.8)	0	1(1.8)	0
Injury, Poisoning, Procedural complication	0	0	0	2(4.9)	0	1(1.8)	0	0	0
Investigations	0	0	0	0	1(2.4)	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	1(1.8)	0	0
Musculoskeletal, Connective tissue disorder	0	0	0	0	1(2.4)	0	0	1(1.8)	0
Nervous system disorders	2(5.0)	3(7.3)	2(5.0)	2(4.9)	8(19.5)	2(3.6)	4(7.1)	5(8.9)	3(5.4)
Renal and urinary disorders	0	0	0	0	0	0	0	1(1.8)	0
Reproductive system and breast disorders	1(2.5)	0	0	0	0	0	0	1(1.8)	0
Respiratory, Thoracic, Mediastinal	1(2.5)	0	3(7.5)	0	0	1(1.8)	0	0	0
Skin and subcutaneous tissue disorders	0	0	1(2.5)	2(4.9)	3(7.3)	0	1(1.8)	0	0

Trt A=IBU+PHE+CHLOR without PG - Fasted, Trt B=IBU+PHE+CHLOR without PG - Fed, Trt C=Single Entities - Fasted

Trt D=IBU+PHE+CHLOR with PG - Fasted, Trt E=IBU+PHE+CHLOR with PG - Fed, Trt F=Motrin IB - Fasted

\*\* A subject may have multiple AEs for each system organ class (SOC). The number of AEs includes ALL events. The number of subjects, however, counts a subject only ONCE within each SOC.

Table 9 Subjects reporting AEs by SOC and PT versus Treatment and Study (Original and New Study Data)

Adverse Events(AEs) (by MedDRA Version 9.0/12.1) SOC and Preferred Term	Original Data			New Safety Data					
	AD0505			AD0606		AD0810			
	Trt A	Trt B	Trt C	Trt A	Trt D	Trt D	Trt E	Trt C	Trt F
N	40	41	40	41	41	56	56	56	56
ANY ADVERSE EVENT	7(17.5)	5(12.2)	7(17.5)	9(22.0)	12(29.3)	7(12.5)	5(8.9)	8(14.3)	6(10.7)
Eye disorders	0	0	0	1(2.4)	0	0	0	0	1(1.8)
Dry eye	0	0	0	1(2.4)	0	0	0	0	1(1.8)
Gastrointestinal disorders	3(7.5)	1(2.4)	2(5.0)	2(4.9)	1(2.4)	3(5.4)	2(3.6)	2(3.6)	2(3.6)
Dyspepsia	1(2.5)	1(2.4)	1(2.5)	0	0	0	0	0	0
Nausea	1(2.5)	0	1(2.5)	0	1(2.4)	2(3.6)	1(1.8)	1(1.8)	2(3.6)
Vomiting	1(2.5)	0	0	0	0	0	1(1.8)	0	0
Abdominal discomfort	0	0	0	0	0	0	0	1(1.8)	0
Constipation	0	0	0	1(2.4)	0	0	0	0	0
Diarrhoea	0	0	0	1(2.4)	0	1(1.8)	0	0	0
General disorders, Administration site	0	1(2.4)	0	3(7.3)	3(7.3)	0	1(1.8)	0	0
Fatigue	0	1(2.4)	0	0	0	0	1(1.8)	0	0
Pain	0	0	0	1(2.4)	3(7.3)	0	0	0	0
Vessel puncture site bruise	0	0	0	2(4.9)	0	0	0	0	0
Infections and infestations	0	0	0	0	0	1(1.8)	0	1(1.8)	0
Nasopharyngitis	0	0	0	0	0	0	0	1(1.8)	0
Rhinitis	0	0	0	0	0	1(1.8)	0	0	0
Injury, Poisoning, Procedural complications	0	0	0	2(4.9)	0	1(1.8)	0	0	0
Catheter site pain	0	0	0	1(2.4)	0	0	0	0	0
Contusion	0	0	0	1(2.4)	0	0	0	0	0
Skin laceration	0	0	0	0	0	1(1.8)	0	0	0
Investigations	0	0	0	0	1(2.4)	0	0	0	0
Blood pressure decreased	0	0	0	0	1(2.4)	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	1(1.8)	0	0
Decreased appetite	0	0	0	0	0	0	1(1.8)	0	0

Trt A=IBU+PHE+CHLOR without PG - Fasted, Trt B=IBU+PHE+CHLOR without PG - Fed, Trt C=Single Entities - Fasted Trt D=IBU+PHE+CHLOR with PG - Fasted, Trt E=IBU+PHE+CHLOR with PG - Fed, Trt F=Motrin IB - Fasted

\*\* A subject may have multiple AEs for each system organ class (SOC). The number of AEs includes ALL events. The number of subjects, however, counts a subject only ONCE within each SOC

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

Adverse Events(AEs) (by MedDRA Version 9.0/12.1) SOC and Preferred Term	Original Data			New Safety Data					
	AD0505			AD0606		AD0810			
N	Trt A	Trt B	Trt C	Trt A	Trt D	Trt D	Trt E	Trt C	Trt F
N	40	41	40	41	41	56	56	56	56
Musculoskeletal, Connective tissue disorder	0	0	0	0	1(2.4)	0	0	1(1.8)	0
Arthralgia	0	0	0	0	0	0	0	1(1.8)	0
Neck pain	0	0	0	0	1(2.4)	0	0	0	0
Nervous system disorders	2(5.0)	3(7.3)	2(5.0)	2(4.9)	8(19.5)	2(3.6)	4(7.1)	5(8.9)	3(5.4)
Dizziness	1(2.5)	2(4.9)	0	2(4.9)	4(9.8)	1(1.8)	3(5.4)	4(7.1)	2(3.6)
Headache	1(2.5)	1(2.4)	2(5.0)	0	4(9.8)	1(1.8)	4(7.1)	1(1.8)	1(1.8)
Renal and urinary disorders	0	0	0	0	0	0	0	1(1.8)	0
Pollakiuria	0	0	0	0	0	0	0	1(1.8)	0
Reproductive system and breast disorders	1(2.5)	0	0	0	0	0	0	1(1.8)	0
Metrorrhagia	1(2.5)	0	0	0	0	0	0	0	0
Vaginal discharge	0	0	0	0	0	0	0	1(1.8)	0
Vulvovaginal discomfort	0	0	0	0	0	0	0	1(1.8)	0
Respiratory, Thoracic, Mediastinal	1(2.5)	0	3(7.5)	0	0	1(1.8)	0	0	0
Dry throat	1(2.5)	0	0	0	0	0	0	0	0
Cough	0	0	1(2.5)	0	0	1(1.8)	0	0	
Nasal congestion	0	0	1(2.5)	0	0	0	0	0	0
Pharyngolaryngeal pain	0	0	1(2.5)	0	0	0	0	0	0
Rhinorrhoea	0	0	1(2.5)	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	1(2.5)	2(4.9)	3(7.3)	0	1(1.8)	0	0
Cold sweat	0	0	0	0	0	0	1(1.8)	0	0
Erythema	0	0	0	2(4.9)	3(7.3)	0	0	0	0
Swelling face	0	0	1(2.5)	0	0	0	0	0	0

Trt A=IBU+PHE+CHLOR without PG - Fasted, Trt B=IBU+PHE+CHLOR without PG - Fed, Trt C=Single Entities - Fasted Trt D=IBU+PHE+CHLOR with PG - Fasted, Trt E=IBU+PHE+CHLOR with PG - Fed, Trt F=Motrin IB - Fasted

\*\* A subject may have multiple AEs for each system organ class (SOC). The number of AEs includes ALL events. The number of subjects, however, counts a subject only ONCE within each SOC

*MO Comment. AEs in Table 9 show that safety of combination product is consistent with that for single ingredient products. The most common adverse events were headache, nausea, and dizziness. There were no serious adverse events or deaths.*

### 7.1.2 Categorization of Adverse Events

Adverse events from studies AD-05-05, AD-06-06 and AD-08-10 are summarized below.

Study AD-05-05 (NDA 22-113): Throughout the study, 15 of 41 (37%) subjects reported 21 AEs. Two subjects reported AEs in two periods and 1 subject reported AEs in 3 periods. The incidence was low for all AEs. The most common AEs among all treatments were headache (4 incidences across treatments), followed by dizziness and dyspepsia (3 incidences across treatments for each). All but 2 AEs were rated as mild; the other two were rated as moderate. All but 2 AEs (fatigue and dizziness) were found by the investigator to be unrelated to the study medications. Seven AEs were reported by 7 subjects (17.5%) following the caplet fasted treatment, 5 AEs were reported by 5 subjects (12.2%) following the caplet fed treatment, and 9 AEs were reported by 7 subjects (17.5%) following the single entity treatment. No notable differences among the treatments were seen in the individual AE rates.

AD-06-06: Throughout the study, 15 of 41 (37%) subjects reported 29 AEs, 6 of whom reported AEs in more than one period. The incidence of AEs for both treatments was relatively low, with dizziness and headaches being the most frequent (2 incidents following treatment with IBU/PE/CHLOR without PG and 8 incidents following treatment with the PG formulation). All but 4 AEs were rated as mild; the other 4, all with PG formulation, were rated as moderate. Twelve of the 29 AEs (3 dizziness, 3 headache, 1 each of neck pain, decreased blood pressure, erythema, dry eye, constipation, and diarrhea) were considered by the investigator to be related to the study medications. Twelve AEs were reported by 9 subjects (22.0%) following the combination caplet formulated without PG and 17 AEs were reported by 12 subjects (29.3%) following treatment with the combination caplet formulated with PG. No notable differences between the formulations were seen within the individual AE rates, with the possible exception of headache.

AD-08-10: Eighteen of 56 (32%) subjects reported 38 AEs. Seven (12.5%) subjects reported AEs during the IBU/PE/CHLOR caplet (fasted) treatment period, 5 (8.9%) during the IBU/PE/CHLOR (fed) treatment period, 8 (14.3%) during the co-administered single entities (fasted) treatment period, and 6 (10.7%) during the Motrin IB tablet (fasted) treatment period. Dizziness, headache and nausea were the most common AEs during the study. Except for one AE rated moderate in severity, all were rated as mild. Twenty-one AEs (8 dizziness, 4 nausea, 3 headaches, 1 each of diarrhea, decreased appetite, fatigue, abdominal discomfort, cold sweats, and pollakiuria) were considered by the investigator to be related to study medications.

*MO Comment. The common adverse events reported in these studies are consistent with the known profiles for IBU, PE, and CHLOR.*

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

NA

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 10 Numbers of Subjects in Clinical Studies

No. of subjects randomized	IBU/PE/CHLOR fasted without PG	IBU/PE/CHLOR fed without PG	IBU/PE/CHLOR fasted with PG	IBU/PE/CHLOR fed with PG	Motrin IB fasted	Motrin IB + Sudafed PE + Chlor-Trimeton Allergy fasted
AD-05-05 (n=41)	40	41	-	-	-	40
AD-06-06 (n=42)	41	-	41	-	-	-
AD-08-10 (n= 56)	-	-	56	56	56	56
Total	81	41	97	56	56	96

The numbers of subjects exposed to each treatments is shown by study in Table 10. A total of 139 subjects participated in the 3 PK studies.

Table 11 Demographics

Study No.	Number entered	Age (yrs) Range (Mean)	Weight (lbs) Range (Mean)	Gender % M/F	Race <sup>1</sup> (%) C/B/A/O	Ethnicity <sup>2</sup> (%) NonH/H
AD-05-05	41	18-42 (26.7)	106-207 (151.5)	46 / 54	78 / 17 / 5 / 0	78 / 22
AD-06-06	42	18-45 (32.6)	105-202 (158.0)	64 / 36	88 / 12 / 0 / 0	79 / 21
AD-08-10	56	18-45 (28.7)	(109-258) (163.9)	63 / 38	88 / 9 / 0 / 4	96 / 4

<sup>1</sup>C/B/A/O = Caucasian/Black/Asian/Other

<sup>2</sup>NonH/H = Non-Hispanic/Hispanic

Subject demographics is shown in Table 11.

### 7.2.2 Explorations for Dose Response

NA.

### 7.2.3 Special Animal and/or In Vitro Testing

NA

### 7.2.4 Routine Clinical Testing

NA

### 7.2.5 Metabolic, Clearance, and Interaction Workup

NA

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

NA

## 7.3 Major Safety Results

### 7.3.1 Deaths

No deaths were reported in studies AD-05-05, AD-06-06 or AD-08-10.

### 7.3.2 Nonfatal Serious Adverse Events

No nonfatal serious adverse events were reported in studies AD-05-05, AD-06-06 or AD-08-10.

### 7.3.3 Dropouts and/or Discontinuations

Table 12 Subject Enrollment in Clinical Trials

Study No.	Number Entered	Number Completed	Number Discontinued	Reason for Discontinuation
AD-05-05	41	40	1	Withdrew consent (1)
AD-06-06	42	40	2	Lost to Follow-up (1) Withdrew consent (1)
AD-08-10	56	56	0	---

Forty-one subjects were enrolled in study AD-05-05. In addition, 98 additional subjects were enrolled in studies AD-06-06 and AD-08-10. In total, 139 subjects participated in the 3 PK studies. In the clinical trials AD-05-05, AD-06-06 and AD-08-10, there were three subjects who discontinued, of whom two withdrew consent and one was lost to follow-up. One of the subjects withdrew due to difficulty with blood draws and the other 'withdrew voluntarily'. No further explanation was provided.

### 7.3.4 Significant Adverse Events

none

### 7.3.5 Submission Specific Primary Safety Concerns

none

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Headache, dizziness, and nausea were the most common adverse events reported in the PK trials. Other adverse events characteristic of each of the active ingredients in the combination are described below.

#### **Ibuprofen**

The most frequently reported AEs associated with NSAID use involve the gastrointestinal (GI) tract, such as dyspepsia, and abdominal pain. Serious AEs such as

peptic ulcer and GI bleeding can occur. There is an increased incidence of cardiovascular events associated with use of NSAIDs at higher than OTC doses. Central nervous system effects, such as headache, dizziness, or nervousness are also reported. Renal insufficiency and renal failure and dermatologic (rash) adverse events are also reported. The incidence and severity of AEs are generally dose and duration of use dependent. The agency believes the overall benefit versus risk profile for the non-prescription NSAIDs remains favorable when they are used according to the labeled directions. When using low dose aspirin for cardioprotection, and depending on the timing of the dosing of ibuprofen, there can be an interference with aspirin's antiplatelet effect.

### **Phenylephrine**

Sympathomimetic drugs like phenylephrine can be associated with AEs such as anxiety, nervousness, tremor, hallucinations, seizures, pallor, respiratory difficulty, and cardiovascular events. In low-therapeutic doses, PE causes little central nervous system stimulation, though a few patients may be sensitive to this effect. As with other sympathomimetic drugs, PE should be used with caution in hypertensive subjects, diabetes mellitus, ischemic heart disease, or prostatic hypertrophy.

### **Chlorpheniramine**

Chlorpheniramine is a first-generation antihistamine. The most common AEs associated with first-generation antihistamines are associated with central nervous system depression, including drowsiness, somnolence, asthenia, dizziness, and loss of coordination. First-generation antihistamines may also stimulate the CNS, a paradoxical response that is more commonly seen in children. Other AEs include headache, psychomotor impairment, and anti-muscarinic effects such as dry mouth, urinary difficulty/retention, and constipation. Gastrointestinal effects are seen less often, but could include nausea, vomiting, diarrhea, and epigastric pain. Palpitations and arrhythmias have been reported occasionally with most antihistamines.

## **7.4.2 Laboratory Findings**

Studies AD-05-05, AD-06-06 and AD-08-10 included a pre-study laboratory examination to determine study eligibility. No post-study laboratory examinations were performed.

## **7.4.3 Vital Signs**

None of the VS readings was abnormal by a clinically significant amount in Studies AD-05-05, AD-06-06, and AD-08-10.

#### 7.4.4 Electrocardiograms (ECGs)

ECGs were recorded at the baseline and at the end of the study for study AD-05-05. There were no clinically significant changes in ECGs during the study (see Dr. Osborne's review). ECGs were not obtained in the other two studies.

#### 7.4.5 Special Safety Studies/Clinical Trials

NA

#### 7.4.6 Immunogenicity

NA

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

NA

#### 7.5.2 Time Dependency for Adverse Events

NA

#### 7.5.3 Drug-Demographic Interactions

NA

#### 7.5.4 Drug-Disease Interactions

NA

#### 7.5.5 Drug-Drug Interactions

NA

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

NA

#### 7.6.2 Human Reproduction and Pregnancy Data

There was no new reproduction or pregnancy data submitted to support this application. The proposed label warns pregnant and breastfeeding women to ask a health professional before use, and warns pregnant women to not use ibuprofen in the last 3 months of pregnancy unless directed by a doctor to do so, since it (ibuprofen) may cause problems in the unborn child or complications during delivery.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

Ibuprofen is approved for use in children down to 6 months of age. Phenylephrine and chlorpheniramine have been used in children as single ingredients or in combinations as cough, cold products. There were no literature references submitted that discussed an effect on growth.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See Section 9.1.

### 7.7 Additional Submissions / Safety Issues

None

## 8 Postmarket Experience

The Sponsor submitted a safety update using two safety databases, AERS (covering the period July 1, 2007 – March 31, 2010) and the Sponsor database (covering October 1, 2007 – January 1, 2011). No triple combination product containing IBU, CHLOR and PE is marketed anywhere in the world, so there is no post-marketing experience with such a product. However, the Sponsor searched the two safety databases for cases with mentions of all three drugs.

For this update, 11 new spontaneous AE reports, documenting a patient's exposure to IBU, PE and CHLOR, at any dose, were identified in the two databases. Nine cases were identified in AERS and the remaining 2 were identified in the sponsor database. All nine of the AERS cases were serious, including 5 hospitalizations and one death in a six year-old.

### **Sponsor Safety Database**

Case 20100068653 reports a 6 year old female patient who was given cetirizine hydrochloride, IBU and APAP for fever, cold symptoms and allergies. The child developed a fever of 106 degrees despite using the products. She was taken to the emergency room and was told it was "probably a strep infection." The mother reported that she took her daughter to the Emergency Room at the time of the fever as she seemed unresponsive the morning after taking cetirizine hydrochloride, and alternating IBU and APAP in addition to APAP/CHLOR/dextromethorphan/PE. The child was discharged home and treated with an unspecified antibiotic. After stopping all of the products the symptoms resolved within a few days and she fully recovered.

*MO Comment. The child's symptoms were likely due to an infection and high fever which responded to the antibiotic.*

Case HQ8625020NOV2001 reports a 44 year old female patient who took IBU, PE and CHLOR for 2 weeks and went to the emergency department on [REDACTED] (b) (6) after experiencing a headache, right- sided pain and tingling, left- sided weakness and tingling in her extremities and lips, sensitivity to noise and lights and vision blackness. The patient was hospitalized for possible stroke. There was no facial, palatal, or lingual weakness. Carotid pulsations were felt bilaterally and no bruits were heard over the neck or head. Muscle strength appeared to be normal in upper and lower extremities. Sensory examination and cerebellar tests were within normal limits. On [REDACTED] (b) (6) a neurologic review of the patient's MRI, MRA and CT Scan revealed no abnormalities. The physician suggested the patient's symptoms were "very likely psychogenic, related to her underlying bipolar disorder." Medications included Axotal, levothyroxine, nasal preparations, nortriptyline, salbutamol and zolmitriptan.

*MO Comment. The etiology of the patient's symptoms is unclear. The subject could have experienced a TIA or migraine accompanied by neurologic symptoms (note that the patient's medications included a triptan).*

### **AERS**

5814820 49 yo male, taking Alka Seltzer Plus (CHLOR, ACETAMINOPHEN, PE) for cold, experienced dizziness, gait disturbance (difficulty walking). During hospital stay, developed nervous system disorder. Discharged, referred to rehab, discontinued Alka Seltzer Plus, unknown continuing medication for neurological disorder. Concomitant medical problems: Charcot-Marie-Tooth Disease, back pain, neck pain, acid reflux, hypertension and hyperlipidemia. Concomitant medications: acetaminophen and chlorphenamine and phenylephrine, amlodipine, carisoprodol, hydrochlorothiazide, ibuprofen, lisinopril, ranitidine, simvastatin, tizanidine.

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

*MO Comment. Dizziness may have been attributed to the Alka Selzer Plus product but any persisting gait disturbances is most likely due to the subject's preexisting neurological conditions.*

5736878 20 yo female, experienced an allergic reaction to the antihistamine in the product (provisional diagnosis by the ER physician), was treated with Ativan and "Something else". Report states she almost passed out and was flailing about. AE terms include: loss of consciousness, dyskinesia, reaction to drug excipients, tremor, drug administration error, aggression, contraindication to medical treatment. Suspect Drug #1 NyQuil Cold/Flu, pseudoephedrine free (paracetamol 325 mg, dextromethorphan hydrobromide 15 mg, doxylamine succinate 6.25 mg); Suspect Medication #2 Advil; Suspect Drug #3: Alka-Seltzer Plus (phenylpropanolamine bitartrate, chlorphenamine maleate, acetylsalicylic acid). Concomitants meds: acetaminophen and chlorphenamine and phenylephrine, ibuprofen

*MO Comment. The reactions are possibly related to CHLOR or doxylamine.*

6616728 a 66 yo female, was injected with Aredia (pamidronate) and Zometa (zoledronate) for treatment of bone metastases and multiple myeloma (diagnosed in 2001) and developed osteonecrosis of the jaw (diagnosed 2007). Patient experienced central venous catheterization, hypothyroidism, neuropathy abscess, abscess drainage, anhedonia, anxiety, asthenia, back pain, bone disorder, chest pain, disability, dyspnoea, fatigue, fistula, gastric disorder, headache, herpes zoster, hypoaesthesia, injury intervertebral disc, disorder musculoskeletal, chest pain, musculoskeletal discomfort peripheral, oestrogen deficiency, osteoarthritis, osteomyelitis, osteonecrosis, pain, pain in jaw, retinal detachment, rib fracture secondary, sequestrum sequestrectomy, swelling, thyroid mass, tremor Concomitants were: acetaminophen, acetaminophen and, hydrocodone, acyclovir, blood, chlorphenamine and phenylephrine and phenylpropanolamine and phenyltoloxamine, clindamycin, dexamethasone, diazepam, epoetin alfa, estrogens conjugated, famotidine, folic acid and iron and vitamin B12 and vitamin C, furosemide, ibuprofen, levothyroxine, loperamide, melphalan, moxifloxacin, ondansetron, pamidronic acid, paroxetine, prednisone, rofecoxib, thalidomide, vitamin, zoledronic acid

*MO Comment. The osteonecrosis is likely due to the zoledronate, and many of the patient's conditions are a result of multiple myeloma or its treatment, and not any of the ingredients in this product.*

5614520 male, unknown age, experienced emotional distress, hypersexuality, injury, major depression, obsessive-compulsive disorder, pathological gambling, suicidal ideation. Started on Mirapex in 1997 for parkinsons, compulsive gambling led to bankruptcy in 2003. Patient discontinued Mirapex in 2005 and gambling, hypersexuality and suicidal ideation are reported to have stopped subsequently

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

within a week. Suspect Drug: Mirapex. Concomitants: acetaminophen, aluminum hydroxide and magnesium hydroxide, aluminum hydroxide and magnesium hydroxide and simethicone, amantadine, azithromycin, bupropion, carbetapentane and phenylephrine and pyrilamine, carbidopa and levodopa, cefalexin, chlorphenamine and phenylephrine and pyrilamine, citalopram, cyclobenzaprine, dicycloverine, entacapone, escitalopram, fluticasone, ibuprofen, levodopa, levofloxacin, loratadine, mirtazapine, naproxen, nefazodone, paroxetine, pramipexole, ropinirole, selegiline, sertraline, sildenafil, tramadol, trazodone, trihexyphenidyl, venlafaxine, vitamin.

*MO Comment. There have been reports of compulsive gambling and hypersexuality associated with Mirapex.*

6558635 a 6 yo male, experienced death. Primary suspect drug listed as Children's Motrin. Report was "received following a JAN-2010 voluntary recall of certain lots of MOTRIN for uncharacteristic taste and smell and a SEP-2009 of Children's TYLENOL products for possible exposure of bulk material to B. Cepacia". The patient's medical history and concurrent conditions included anemia and a heart murmur. At home and at school, the patient was treated with JAN-2010 recalled product Children's TYLENOL Bubblegum (acetaminophen, 80mg/tablet, meltaways, oral, batch AHA069, lot recalled) and SEP-2009 recalled product Children's TYLENOL Plus Cold Multi-Symptom Grape (apap/CHLOR/dextromethorphan/PE oral suspension, batch AJM403, lot not recalled), Children's MOTRIN Berry Oral, (ibuprofen, 100mg/5ml, suspension, batch AHM384, product not recalled) and Children's MOTRIN Bubblegum Oral (ibuprofen, 100mg/5ml, suspension, batch ADM038, product not recalled). In [REDACTED] (b) (6) the patient was admitted to the hospital and diagnosed with pneumonia, hypotension and thrombocytopenia. Patient was transferred to another hospital and died with a diagnosis of renal failure and sepsis. Preferred terms: pneumonia, product quality issue, renal failure, sepsis, thrombocytopenia, abdominal pain upper, diarrhoea, hypotension, nausea, product odour abnormal, transmission of an infectious agent via a medicinal product, vomiting, acetaminophen, acetaminophen and chlorphenamine and phenylephrine, ibuprofen. Blood cultures identified Burkholderia Cepacia in the blood, sputum and urine.

*MO Comment. The death case 6558635 involved a 6 yo child with a history of anemia and heart murmur, who died of sepsis from B. Cepacia and who was documented to have taken Children's Motrin and Tylenol products, where one of the recalls (Children's Tylenol) was for possible exposure of bulk material to B. Cepacia. Although the death may be attributed to the recalled product, it was a product quality issue and not an intrinsic risk attributable to any of the product ingredients.*

6241804 1 yo male with bilateral renal dysplasia and bilateral ureteropelvic junction obstruction at birth in 1994 with subsequent development of end stage renal

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

disease. bilateral nephrectomies, renal transplant which later failed, placed on peritoneal dialysis. On Epogen therapy for dialysis from 12 days after birth. In 2007 experienced uncontrolled hypertension and had a cerebral infarction, encephalomalacia, respiratory distress, transplant rejection, convulsion, hyperparathyroidism, secondary hypertension, infection, leukopenia, therapeutic response decreased, thrombocytopenia. Anemia continued through 2009, with dose of Epogen reduced. Epogen listed as primary suspect drug. Concomitants: acetaminophen, albumin, albuterol, calcitriol, calcium carbonate, chlorphenamine and phenylephrine and phenylpropanolamine and phenyltoloxamine, citric acid and sodium citrate, diphenhydramine, docusate, epoetin alfa, fluticasone, guaifenesin, ibuprofen, iron sucrose, levalbuterol, macrogol, mupirocin, ranitidine, sevelamer, sodium polystyrene, sulfonate, vitamin with iron.

*MO Comment. This case 6241804 of cerebral infarction in a child was likely due to uncontrolled hypertension due to his kidney disease.*

*MO Comment. In the following three AERS cases, there are numerous concomitant medications or underlying medical conditions that could have caused the events such that it is not possible to assign causality to IBU, PE, or CHLOR.*

5701916 58 yo male, who received Diovan (valsartan) in 2006 for hypertension and proteinuria and Lotrel (amlodipine and benazepril) developed nerve damage from his back down to his legs and his knee collapsed. Patient has multiple medical problems including a three vessel aortic coronary bypass, narcolepsy, hypertension, fibromyalgia, diabetes, arthritis, hyperlipidemia, stomach problems, hay fever, hypothyroidism and allergies to multiple medications. Physician reported that subject is also allergic to Diovan and Lotrel; knee injury is not suspected to be due to Diovan. Outcome is unknown. Preferred terms drug hypersensitivity, joint injury, nerve injury. Concomitants: acetaminophen and chlorphenamine and phenylephrine, acetaminophen and hydrocodone, amlodipine and benazepril, aspirin, atenolol, calcium and magnesium and zinc, colestipol, estazolam, folic acid, hydrochlorothiazide, ibuprofen, insulin, insulin detemir, levothyroxine, lisinopril, loperamide, metaxalone, niacin, orphenadrine, potassium chloride, ranitidine, sildenafil, spirulina spp. testosterone, valsartan, vardenafil, vitamin B, vitamin C, zolpidem.

6199499 36 yo obese female in 2005 took Ketek (telithromycin) and other medications (including IBU, CHLOR, and PE) for URI. Was subsequently hospitalized for IV levaquin. Patient improved and was discharged with diagnoses of fatigue, malaise, and anxiety. She continued to feel unwell with fatigue and cough and had mildly elevated transaminases. She underwent a laparoscopic cholecystectomy and was found to also have fatty infiltration of the liver and chronic triaditis. Concomitants were: acetaminophen, alprazolam, aluminum hydroxide and magnesium hydroxide and simethicone, antibiotics-verbatim, chlorphenamine and dextromethorphan and

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

phenylephrine, doxycycline, ibuprofen, laxatives-verbatim, levofloxacin, promethazine, telithromycin, zolpidem.

6369839 male aged 45 who was treated in 2002 for weight loss with SEROQUEL (quetiapine fumarate) and ZYPREXA (olanzapine). Patient experienced pancreatitis in 2004 and diabetes in 2003. Patient has diagnosis of paranoid schizophrenia.

Preferred terms: hypoglycaemia, pancreatitis, type 2 diabetes, mellitus.

Concomitants: amlodipine, brimonidine, carisoprodol, cetirizine, chlorphenamine and dextromethorphan and phenylephrine, diazepam, dorzolamide and timolol, enalapril, glyburide, haloperidol, ibuprofen, indometacin, latanoprost, metaxalone, naproxen, olanzapine, prednisolone, quetiapine, risperidone, topiramate, valproic acid.

*MO Comment. No new safety issues are raised for a combination IBU/CHLOR/PE product by the two spontaneous reports from the Sponsor database or from the nine reports in AERS from July 1, 2007 to March 31, 2010.*

## 9 Appendices

### 9.1 Literature Review/References

This submission included an update of safety from the literature beginning December 12, 2007 (the date where the last literature review ended).

A literature search was performed on the combination of “ibuprofen” and “phenylephrine” and “chlorpheniramine” utilizing the following databases: Medline, Biosis Previews, Toxfile, EMBASE, International Pharmaceutical Abstracts, SciSearch and Derwent Drug File over the period from December 12, 2007 to January 11, 2011. The search did not find any references concerning the safety of the drug combination. Another search was conducted for safety-related literature of each of the individual active ingredients: ibuprofen, chlorpheniramine and phenylephrine. The latter search yielded 24 papers describing events distributed among various organ systems or subjects summarized below.

#### Misuse, Abuse and Overdose

**Dutch** 2008 presented two case reports of perforated gastric ulcers from recreational misuse of an ibuprofen/codeine product (200 mg IBU/12.8 mg codeine) in Australia. This is the highest dose of codeine available without a prescription in Australia. Both cases were treated surgically; one recovered and one lost to follow-up.

*MO Comment. Perforated gastric ulcers are a known adverse effect of NSAIDs for which the product is already labeled. Codeine was the likely misuse target in these two cases.*

**Lamkin** 2009 presented a case report of multiple drug overdose with cocaine (two lines), alprazolam (unknown amount) and IBU (200 to 300 tablets). A mild metabolic acidosis was treated and patient recovered in 24 hours.

*MO Comment. Metabolic acidosis is known to be associated with severe overdoses of ibuprofen (see ibuprofen in Micromedex Toxicologic Managements).*

**Murao** et al. 2009 presented a case report of generalized convulsions and mixed acidosis in a 35 year old male taking an OTC antitussive combination product sold in Japan, containing dihydrocodeine phosphate, methylephedrine, chlorpheniramine, and caffeine. Twelve hours later he recovered consciousness and EEG findings were normal 10 days later. During event, the chlorpheniramine blood concentration in the present case was 0.43 mg/l, which is more than 20 times greater than the mean peak plasma level measured after a single therapeutic dose. Pinpoint pupils also indicated poisoning by dihydrocodeine. The patient sometimes took more than the recommended daily dose of the antitussive. Convulsions were attributed to overdose of

chlorpheniramine, although possible contributions to the convulsions by dihydrocodeine or methylephedrine were acknowledged.

***MO Comment.** Again this case primarily involved misuse or abuse of a combination product containing dihydrocodeine which is not an ingredient in the present product. Convulsions have been reported with antihistamine overdose.*

**Logan** 2009 presented a case series of eight drivers arrested for driving under the influence from effects of dextromethorphan and CHLOR, which are compared to another four arrested drivers under the influence of dextromethorphan alone. Drivers generally displayed symptoms of CNS depressant intoxication, inattention, and grossly impaired driving. There were no major distinguishing features between cases with both dextromethorphan and CHLOR and those with dextromethorphan alone. In the combined dextromethorphan/chlorpheniramine cases, blood dextromethorphan concentrations ranged from 150 to 1220 ng/mL (n = 8; mean 676 ng/mL, median 670 ng/mL), and chlorpheniramine concentrations ranged from 70 to 270 ng/mL (n = 8; mean 200 ng/mL, median 180 ng/mL). The four cases without chlorpheniramine present had blood dextromethorphan concentrations between 190 and 1000 ng/mL (mean 570 ng/mL, median 545 ng/mL). The CHLOR levels in the present case series were 7 to 27 times therapeutic levels (which are about 10 ng/ml, the mean plasma concentration at 3 hr after a 6 mg oral dose).

CHLOR can cause a short-term impairment of driving ability (Theunissen et al. 2006; Vermeeren et al. 1998). Using an actual on-road driving performance test, Theunissen et al. (2006) found a significant deterioration in driving performance on the first day after administration of two 6 mg CHLOR tablets bid for 8 days, but the effects disappeared after 8 days of administration. Vermeeren et al. (1998) administered 8 or 12 mg CHLOR doses to 24 subjects at bedtime, followed the next morning by a dose of the nonsedating antihistamine terfenadine. Subjects then completed an on-road driving test. They concluded that there was no residual effect the next day after a single bedtime dose of either 8 or 12 mg sustained release CHLOR.

***MO Comment.** Dextromethorphan is a known drug of abuse because of its intoxicating, hallucinogenic, and dissociative effects. OTC cough-cold preparations combine dextromethorphan with the antihistamine chlorpheniramine, which may add a sedating component to the drug experience. In some cases, CHLOR has a paradoxical stimulating effect. There are relatively few reports of deaths or intoxications attributed specifically to chlorpheniramine alone.*

**Tashiro et al.** 2008 also tested simulated driving after administration of D-chlorpheniramine 6 mg or placebo in 14 male volunteers. The number of lane deviations significantly increased in the D-chlorpheniramine condition compared with the placebo condition ( $p < 0.01$ ). Subjective sleepiness was not significantly different between the two drug conditions.

***MO Comment.** Adverse events associated with first generation antihistamines include drowsiness and psychomotor impairment. The label includes a warning for individuals to be careful when driving a motor vehicle or operating machinery.*

**Venkatraman** 2008 presented a case of intentional overdose with lamotrigine (9.2 g), citalopram (220 mg), and chlorpheniramine (54 mg) in a 23 year old female who presented with reduced consciousness, sinus tachycardia and prolonged QTc (>470 ms). Patient recovered.

***MO Comment.** The article notes that lamotrigine exerts its anti-epileptic effect through inhibition of voltage-dependent sodium channels and that it inhibits cardiac rapid delayed rectifier potassium currents (Danielsson et al. 2005), and may cause prolonged QTc in overdose. Citalopram, an SSRI, can also cause cardiac arrhythmia. Catalano et al. (2001) presented a case report of QTc prolongation associated with citalopram overdose. Micromedex also notes that citalopram has dose dependent QT prolongation and that Torsade de Pointes has been reported with use. Both of these ingredients are more likely causes of the QTc prolongation than CHLOR.*

### **Gastrointestinal Effects**

**Singh** 2008 presented a case report of esophageal perforation in an 18 year old male, after a single 200 mg liquid IBU capsule. Two days earlier, had taken another single capsule which became impacted in his esophagus but which passed after several glasses of water. On day of event, capsule became impacted again, but did not pass after several glasses of water, and symptoms of pain, odynophagia, dysphagia and dyspnea increased. The patient was admitted to the ICU, made NPO, and treated with IV fluids, IV antibiotics, and an IV PPI. The patient recovered without surgery.

***MO Comment.** Pill-induced esophageal perforation is a rare but serious complication that has not been previously reported with ibuprofen, according to the author.*

**Hawkey** et al. 2008, TARGET clinical trial in 18,244 diagnosed osteoarthritis (OA) patients comparing lumiracoxib 400 mg qd (n=9117 subjects) with naproxen 500 mg bid (n=4730) or IBU 800 mg tid (n=4397). Objective was to investigate how early a reduction in ulcer complications could be detected with lumiracoxib vs. nonselective NSAIDs. In patients not on low-dose aspirin, there was a significant reduction in all ulcers by day 8 and in ulcer complications by day 16 with lumiracoxib compared with both nonselective NSAIDs combined, and by day 32 (all ulcers) and day 33 (ulcer complications) vs. ibuprofen. In ASA users (24% of the study population, all groups) there was no significant difference in ulcers and ulcer complications between lumiracoxib and either nonselective NSAIDs.

***MO Comment.** This study showed a reduction in ulcers and in their complications with lumiracoxib after short-term durations of treatment as compared to nonselective NSAIDs. However, this reduction was demonstrated in OA patients*

*taking anti-inflammatory doses, where the incidence of GI complications is elevated compared to that associated with OTC dosing.*

### **Anti-Platelet Effects**

**Hong Y** et al. 2008 performed a single-blinded, randomized, three-way crossover study enrolling ten healthy volunteers, to compare single doses of oral ASA (325 mg) and IBU (400 mg) with concomitant administration of ASA (325 mg) and IBU (400 mg). Relatively complete inhibition of platelet aggregation was achieved following ASA treatment (~77% inhibition within 2 hours), and return to baseline values occurred within 72-96 hours after dosing. In contrast, treatment with IBU alone or in combination with ASA produced transient inhibition of platelet aggregation, with complete recovery observed in 6-8 hours.

**Gengo** et al. 2008 performed a single-blinded, randomized, three-way crossover study enrolling ten healthy volunteers, to compare single doses of oral ASA (325 mg) and IBU (400 mg) with overlapping administration of IBU (400 mg) followed by ASA (325 mg) two hours later. Platelet aggregation studies showed that both the magnitude and the duration of aggregation inhibition from ASA 325 mg are reduced significantly by IBU 400 mg taken shortly before the ASA. Within 4 to 6 hours after taking ASA along with IBU, platelet function is not different from measures at drug-free baseline. In addition, a 27 month follow-up study was reported in 28 patients receiving ASA for stroke prophylaxis who reported also regular daily use of IBU or naproxen. Eighteen of these subjects were retested for platelet aggregation after discontinuing the NSAID or taking it at a time to avoid ASA interaction. There was no inhibition of platelet aggregation during the ongoing ASA-NSAID interaction, but removal of the NSAID interaction reliably restored platelet responsiveness to ASA. Thirteen of these 18 patients (72%) had experienced a recurrent ischemic episode while on both ASA and NSAIDs.

**Gladding** et al. 2008 performed a double blind, randomized, crossover study to compare the antiplatelet effects of 6 NSAIDs (IBU 400 mg, indomethacin 25 mg, naproxen 550 mg, tiaprofenic acid 300 mg, sulindac 200 mg, celecoxib 200 mg) and to determine whether they antagonize the antiplatelet effect of ASA 300 mg. The study was performed in 24 healthy volunteers, randomized into one of two groups, each of which took 3 NSAIDs and placebo in random order. On day 1, platelet testing at baseline, then two doses of NSAID at 8 am and 8 pm, followed by platelet testing 12 hr afterwards the next morning. Then the final (4<sup>th</sup>) dose of NSAID was given at 8 am on Day 2, and two hr later, the ASA dose was given. Then platelet function testing again 24 hr later, at 8 am on Day 3. Ibuprofen, indomethacin, tiaprofenic acid, and naproxen all antagonize the antiplatelet effect of aspirin. Ibuprofen and indomethacin taken individually did not have antiplatelet effects at the end of a 12-hour dosing interval (naproxen does). Sulindac and celecoxib did not have significant antiplatelet effect taken individually and did not interfere with the antiplatelet effect of ASA.

*MO Comment. The cardioprotective effect of ASA from inhibition of platelet aggregation is attenuated by co-administration of IBU with ASA. A label warning to this effect is included in the OTC IBU label. The product label for OTC NSAIDs*

*also warns that the risk of stroke may increase if IBU is used more than directed or for longer than directed.*

**Prasad** et al. 2008 studied the effect of ibuprofen on bleeding during periodontal surgery using a case series of ten subjects, each of whom had two surgeries, one with IBU (400 mg given 9hr, 5hr, and 1 hr before surgery) and one without. IBU significantly increased bleeding time and volume.

*MO Comment. This is a well known effect of ASA and NSAID products. Patients are generally advised by their dentists not to take these drugs prior to oral surgery.*

### **Stroke and Cardiovascular Effects**

**Roumie** et al. 2008 performed a retrospective cohort study among 336,906 Tennessee Medicaid enrollees aged 50 to 84 years between January 1, 1999 and December 31, 2004. Those continuously enrolled in Medicaid and without stroke or other serious medical illness in the year before cohort entry were included. The study examined the 7 most common NSAIDs (celecoxib, rofecoxib, valdecoxib, ibuprofen, naproxen, diclofenac, and indomethacin) and defined nonuse of NSAIDs as the reference group. The outcome was hospitalization for an incident cerebrovascular event: ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage. In the 989,826 person-years of follow-up in the study, there were 4354 stroke hospitalizations. There were 4.51 strokes per 1000 person years in the nonuse group, but 5.15 strokes per 1000 person years (adjusted HR 1.28, 95% CI: 1.06, 1.53) with rofecoxib use, and 5.95 strokes per 1000 person years (adjusted HR 1.41, 95% CI: 1.04, 1.91) with valdecoxib use. For IBU, there were 3.96 strokes per 1000 person years (adjusted HR 0.88, 95% CI: 0.73, 1.06). A separate analysis of new users (without NSAID use in the year prior to enrollment) yielded similar results. The authors concluded that an increased risk of incident cerebrovascular event was confirmed for current users of valdecoxib and rofecoxib, but there was no significant increase in the risk of incident stroke associated with use of the other five NSAIDs including IBU.

COPYRIGHT MATERIAL

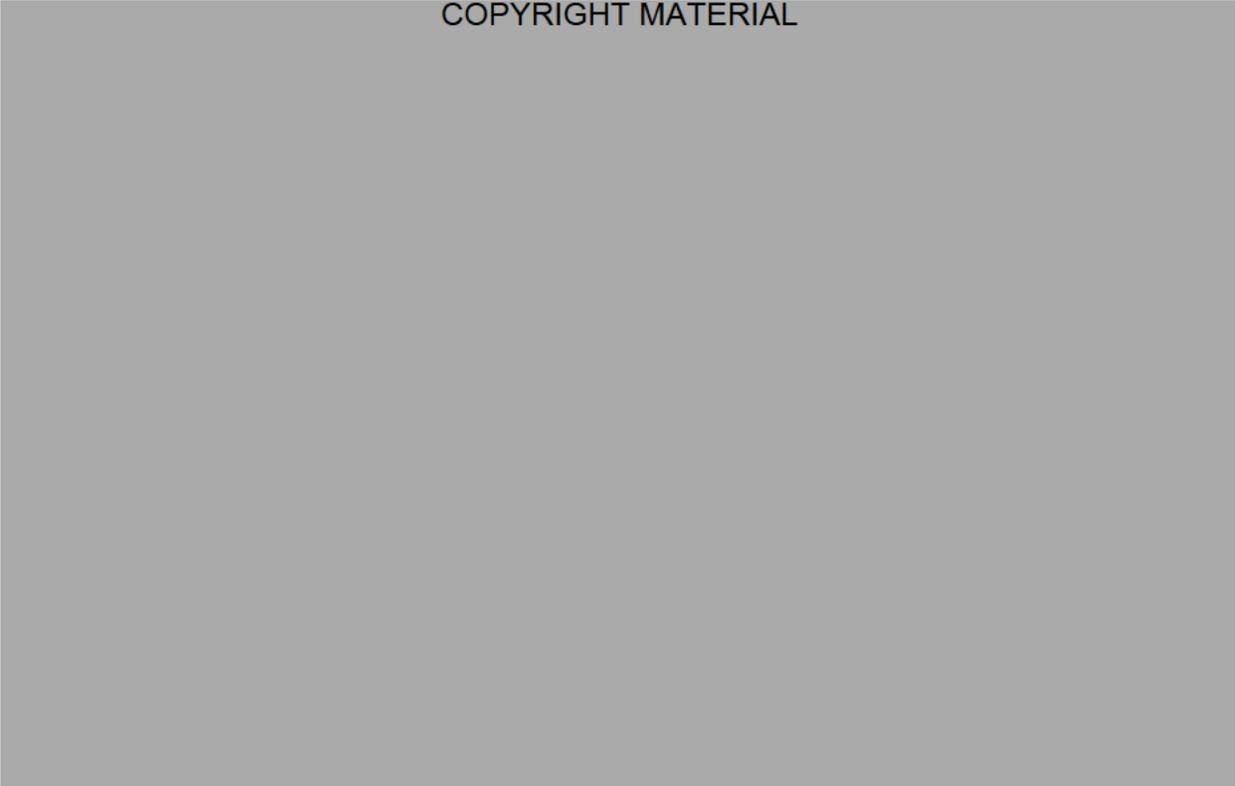


Figure 4 Tennessee Medicaid study of NSAID stroke risk (Roumie et al. 2008)

*MO Comment. Rofecoxib and valdecoxib were withdrawn from marketing in 2004 and 2005, respectively, because of cardiovascular adverse events. The Roumie et al. results indicate an increased risk of stroke for the selective coxibs, rofecoxib and valdecoxib. However, this study found no increased stroke risk for other NSAIDs including IBU compared to non-use.*

**Farkouh** et al. 2008 reported results on BP changes from the TARGET clinical trial in 18,244 diagnosed OA patients comparing lumiracoxib 400 mg qd (n=9117 subjects) with naproxen 500 mg bid (n=4730) or IBU 800 mg tid (n=4397). Mean change from baseline at week 4 for systolic BP was +0.57 mm Hg with lumiracoxib compared with +3.14 mm Hg with ibuprofen (p<.0001) and +0.43 with lumiracoxib compared with +1.80 mm Hg with naproxen (p<.0001).

*MO Comment. The clinical significance of these BP changes is not clear. The TARGET trial previously reported smaller mean changes in systolic and diastolic mean BP with lumiracoxib versus IBU and naproxen, but at 52 weeks as opposed to 4 weeks, 3, 6, and 9 months in the present report.*

**Van Staa** et al. performed a retrospective cohort study using the UK General Practice Research Database, to investigate and compare risks of MI for diclofenac, IBU and

naproxen in primary care use. The study included 729,294 NSAID users and 443,047 controls. The relative rate (RR) for MI increased with cumulative and daily dose (RR = 1.05 with 0–4 prior prescriptions and RR = 1.49 with 30+ prescriptions; RR = 1.05 with daily dose of <1200 mg ibuprofen and RR = 1.96 with dose of  $\geq$ 2400 mg per day; for diclofenac, the RR was 1.13 with <150 mg per day and 2.03 with  $\geq$ 300 mg per day). Diclofenac users had higher risks of MI (RR = 1.21) than ibuprofen (RR = 1.04) or naproxen (RR = 1.03) users, but exposure varied between these drugs. Taking into account these exposure differences, it was found that the risk of MI was comparable in current and past long-term users. The patterns of absolute risks of MI were similar in patients using ibuprofen, diclofenac or naproxen with similar history of NSAID use. There was no statistical difference between ibuprofen, diclofenac and naproxen in the linear trends for cumulative dose or daily dose.

*MO Comment. Two previous studies reported an increased risk of CV events for particular NSAIDs, notably rofecoxib and diclofenac. Kearney et al. (2006) performed a meta-analysis of cardiovascular (CV) events for 138 randomized trials. They found that selective COX-2 inhibitors are associated with increased risk of vascular events, as are high dose ibuprofen (800 mg tid) and diclofenac, but not naproxen. The McGettigan and Henry (2006) meta-analysis similarly found an increased, dose-related risk with rofecoxib during the first month of treatment. Among the older nonselective drugs, diclofenac was found to have the highest relative risk with RR = 1.40 (95% CI, 1.16-1.70). Celecoxib was not associated with an elevated risk, RR = 1.06 (95% CI, 0.91-1.23). The following NSAIDs also had relative risks close to 1: naproxen, RR=0.97 (95% CI, 0.87-1.07); piroxicam, RR=1.06 (95% CI, 0.70-1.59); and ibuprofen, RR=1.07 (95% CI, 0.97-1.18).*

*The van Staa study suggested that the prior studies could not fully account for differences in the use of different NSAIDs in clinical practice, and that there were differences in the uses of different NSAIDs. Compared with ibuprofen, diclofenac was used more by patients with a frequent history of NSAID use and by patients with prior switching between NSAID types (patients who switched may have done so because of adverse events with another NSAID). With respect to daily dose, 0.9% of the ibuprofen prescriptions were for a higher daily dose ( $\geq$ 2400 mg daily), versus 54.3% of diclofenac ( $\geq$ 150 mg) and 65.0% of naproxen ( $\geq$ 1000 mg) prescriptions.*

*The van Staa study found that increasing duration of NSAID use was associated with larger risks of MI, but these risks (associated with long duration use) remained elevated for several years after discontinuing NSAID exposure. The authors suggest that this persistent elevated risk is associated with the underlying conditions for which the drug was prescribed. Diclofenac users had higher risk of MI than naproxen or ibuprofen users, but history of use and prior switching differed between these drugs. The patterns of MI risk were similar between diclofenac, ibuprofen and naproxen after taking into account history of use.*

*Specifically for IBU, there was elevated risk of MI in IBU users of high daily doses but not for those taking lower doses that are consistent with allowed OTC doses.*

COPYRIGHT MATERIAL

**Gislason** et al. 2009 studied the risk of death and hospitalization because of acute myocardial infarction and heart failure (HF) associated with use of NSAIDs in an unselected cohort of patients with HF. The study identified 107,092 patients surviving their first hospitalization because of HF between January 1, 1995, and December 31, 2004, and their subsequent use of NSAIDs from nationwide registries of hospitalization and drug dispensing by pharmacies in Denmark. The hazard ratio (95% CI) for death was 1.70 (1.58-1.82), 1.75 (1.63-1.88), 1.31 (1.25-1.37), 2.08 (1.95- 2.21), 1.22 (1.07-1.39), and 1.28 (1.21-1.35) for rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, and other NSAIDs, respectively. Furthermore, there was a dose-dependent increase in risk of death and increased risk of hospitalization because of myocardial infarction and HF.

*MO Comment. The Gislason et al. study found an elevated risk of death and hospitalization from MI and HF for any use of IBU in those with a history of HF, but when stratified by dose the risks are found to be dose-dependent. At low doses consistent with OTC use ( $\leq 1200$  mg/day) there was no elevated risk of death or of hospitalization for MI, but there was still an elevated risk of hospitalization for HF.*

COPYRIGHT MATERIAL

**Fosbol** et al. 2009 also used the Danish registry to perform a historical cohort study of the risk of death and myocardial infarction associated with the use of NSAIDs by

apparently healthy individuals. Participants in the study were defined as healthy according to a history of no hospital admissions and no concomitant selected pharmacotherapy. The study population consisted 1,028,437 subjects after applying selection criteria. Compared to no NSAID use, hazard ratios (95% confidence limits) for death/myocardial infarction were 1.01 (0.96–1.07) for ibuprofen, 1.63 (1.52– 1.76) for diclofenac, 0.97 (0.83–1.12) for naproxen, 2.13 (1.89–2.41) for rofecoxib, and 2.01 (1.78–2.27) for celecoxib. A dose-dependent increase in cardiovascular risk was seen for selective COX-2 inhibitors and diclofenac. The results include a dose-dependent relationship between NSAID treatment and risk of death and myocardial infarction. In this apparently healthy population, however, the absolute risk of death and cardiovascular events as a result of NSAID intake is low, which was reflected in the high number of patients needed to be treated with NSAIDs to cause harm (>400 needed to be treated for IBU).

COPYRIGHT MATERIAL

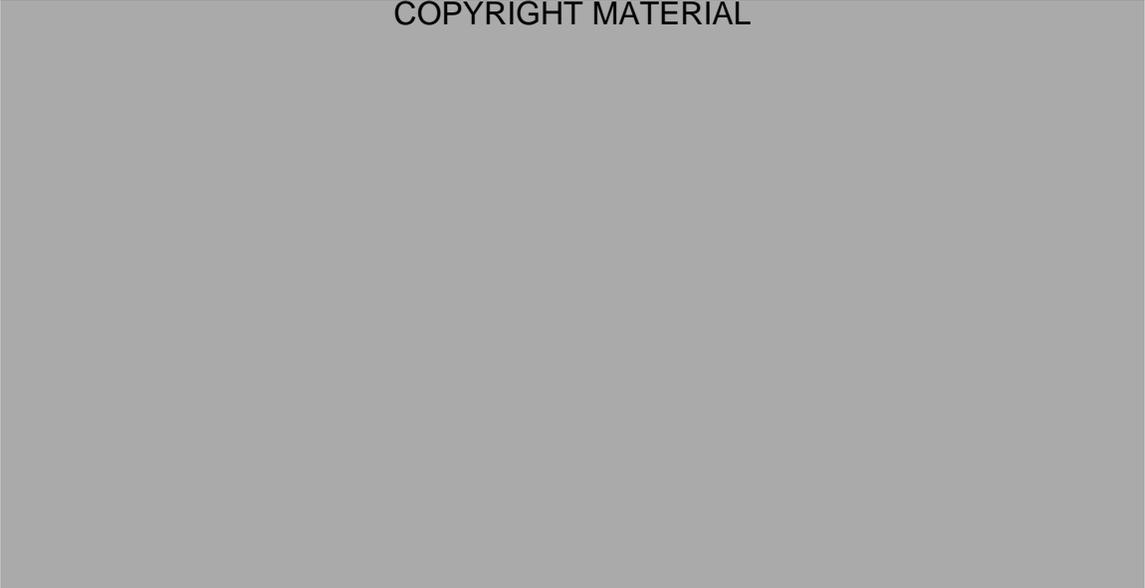


Figure 5 Risk of death or MI. Hazard ratio with exposure to NSAIDs in healthy population of 1,028,437 people; error bars show 95% CI (Fosbol et al. 2009). Use of IBU at OTC doses is not associated with any elevated risk.

*MO Comment. Again, there is a dose dependent risk of cardiac event from NSAID use. IBU and naproxen at OTC doses are not associated with increased risk. There is an increased risk associated with diclofenac, rofecoxib, and celecoxib. Technical issues have been raised about the definitions of the healthy study cohorts and about the possibility of confounding by indication (Moore, 2009; Renner and Brune, 2009).*

**Varas-Lorenzo** et al. 2009 performed an observational cohort study of coxibs and non-selective NSAIDs to compare risks of acute MI. The study identified a cohort of 364,658 individuals aged 40–84 years enrolled in Saskatchewan Health, Canada from 15 November 1999 to 31 December 2001. A nested case–control analysis compared 3252

cases of hospitalized AMI and out-of-hospital CHD deaths with 20,002 controls randomly sampled from the cohort. The incidence of AMI/CHD was 5.1 per 1000 person-years (95%CI: 5.0–5.3). The adjusted ORs (95%CI) of AMI/CHD in current users of individual NSAIDs compared with non-use were: celecoxib (1.11; 0.84–1.47), rofecoxib (1.32; 0.91–1.91), diclofenac (1.02; 0.75–1.38), naproxen (1.57; 0.98–2.52), ibuprofen (1.59; 0.88–2.89), and indomethacin (1.34; 0.81–2.19).

***MO Comment.** This study did not identify an increased risk of hospitalized AMI and out-of-hospital CHD deaths for any of the studied drugs in prescription use, including IBU (95% CI for OR included unity). The lead author is affiliated with Pfizer.*

**Trelle** et al. 2011 performed a meta-analysis of 31 clinical trials, with a total of 116,429 patients and 115,000 patient-yr of follow-up, to study cardiovascular safety of NSAIDs. Study drugs were: naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib, or placebo. Compared with placebo, rofecoxib was associated with the highest risk of myocardial infarction (rate ratio 2.12, 95% CI 1.26 to 3.56), followed by lumiracoxib (2.00, 0.71 to 6.21). Ibuprofen was associated with the highest risk of stroke (3.36, 1.00 to 11.6), followed by diclofenac (2.86, 1.09 to 8.36). Etoricoxib (4.07, 1.23 to 15.7) and diclofenac (3.98, 1.48 to 12.7) were associated with the highest risk of cardiovascular death.

***MO Comment.** The meta-analysis included only two trials with ibuprofen, one in OA patients and one in OA and RA patients utilizing anti-inflammatory doses. For IBU at anti-inflammatory doses 2400 mg/d, this study suggested an elevated risk of MI (1.61, 95%CI 0.50-5.77) cardiovascular death (2.39, 0.69-8.64), or death from any cause (1.77, 0.73-4.30). However, the 95% CI for these rate ratios included unity, There was weak evidence for elevated incidence of stroke (3.36, 1.00 to 11.6) and for the Antiplatelet Trialists' Collaboration composite outcome (2.26, 1.11 to 4.89) of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The OTC label for IBU warns that the risk of heart attack or stroke may increase if you use more than directed or for longer than directed.*

**Nia** et al. 2010 presented a case report of torsades de pointes tachycardia necessitating CPR, thought to be induced by a cold medication containing 200 mg of acetaminophen, 150 mg of ascorbic acid, 25 mg of caffeine, and 2.5 mg CHLOR. The subject was a 40 year old female, smoker, on no permanent medication, unremarkable physical examination, and no prior history of arrhythmia. She had self-medicated at two capsules, three times a day, for some days, until the evening before the event.

***MO Comment.** CHLOR has been shown to cause a dose-dependent block of the delayed rectifier potassium channel and to lengthen the action potential, slow cardiac repolarization, and prolong the QTc interval (Hong and Jo 2009; Salata et al. 1995). Drug concentration was not measured initially, and the patient did not allow genotyping. The reviewer searched the Empirica database for spontaneous reports with CHLOR (as suspect drug) and any of the following terms: torsades, ventricular tachycardia, ventricular fibrillation, and sudden death. After removal of*

*duplicate reports, a total of 5 cases was retrieved: ISR numbers 1993757-0, 7550757-6, 4463908-7, 4349421-6, 7151337-7. All were serious reports, and three were from the literature. Two of the five reports were suicides who ingested multiple drugs. One case was a sudden death which occurred several months after the event and was not related. In every reported cardiac event, there were concomitant drugs which could also have caused or contributed to the event and/or underlying medical conditions.*

## **Renal Effects**

**Lafrance** and Miller 2009 compared risk of acute kidney injury (AKI) between selective and non-selective NSAIDs using a laboratory-based definition of AKI in a large cohort from the U.S. Department of Veterans Affairs health care system. AKI was defined as a creatinine increase of greater than 50%. A retrospective, nested case-control study was performed in a cohort of 1,459,271 new NSAID users, wherein 22,824 cases of AKI and 336 734 matched controls were identified between 2000 and 2006. A higher risk of AKI was found in new users of any single NSAID (adjusted odds ratio = 1.82; 95%CI: 1.68, 1.98) compared to nonusers without recent use. The risk of AKI was generally greater with less selective NSAIDs: rofecoxib (0.95; 0.64, 1.42), celecoxib (0.96; 0.63, 1.47), meloxicam (1.13; 0.63, 2.05), etodolac (1.31; 1.08, 1.59), diclofenac (1.11; 0.84, 1.48), piroxicam (1.53; 1.05, 2.23), salsalate (1.51; 1.22, 1.87), sulindac (1.61; 1.12, 2.30), ibuprofen (2.25, 2.04, 2.49), naproxen (1.72; 1.52, 1.95), high dose aspirin (3.64; 2.46, 5.37), indomethacin (1.94; 1.56, 2.42), keterolac (2.07; 1.78, 2.41). Those using multiple NSAIDs appeared to have higher risk (2.90; 2.62, 3.22).

*MO Comment. The crude average incidence rate of AKI so defined was reported as 3.77 /1,000 person-years (95%CI: 3.72, 3.82). The risk of such AKI was increased by a factor 1.82 for new users of NSAIDs versus non-users.*

*However, the report's conclusion that the risk of AKI is increased for less selective NSAIDs may be confounded by an indication bias. The study stated that coxibs were "usually prescribed to patients with more co-morbidities". The study performed an adjustment for co-morbidities which increased the IBU OR from an insignificant OR=1.24 (95%CI 0.90, 1.70) to a significant OR=2.25 (95%CI 2.04, 2.49). The study conclusion of increased AKI risk for nonselective NSAIDs depends on the adjustment for co-morbidities.*

*A previous epidemiologic study (Schneider et al. 2006), that compared association of selective and nonselective NSAIDs with acute renal failure, did not find an increased risk of acute renal injury from nonselective NSAIDs over selective NSAIDs. This was a nested case-control study of 121,722 new NSAID users older than age 65 years from the administrative health care databases of Quebec, Canada, in 1999–2002. Data for 4,228 cases and 84,540 matched controls were analyzed. The risk of acute renal failure for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted RR = 2.05, 95% CI: 1.61, 2.60) and receded thereafter. The association with acute renal failure within 30 days of therapy initiation was comparable for rofecoxib (RR = 2.31, 95% CI:*

1.73, 3.08), naproxen (RR = 2.42, 95% CI: 1.52, 3.85), and nonselective, non-naproxen NSAIDs (including IBU, RR = 2.30, 95% CI: 1.60, 3.32) but was borderline lower for celecoxib (RR = 1.54, 95% CI: 1.14, 2.09).

*It is known that renal insufficiency and renal failure can occur with NSAID use.*

### **Hepatic Effects**

**Soni et al.** 2009 compared hepatic safety of celecoxib to nonselective NSAIDs diclofenac, IBU and naproxen with a meta-analysis of 41 controlled randomized trials. There were no cases of liver failure, treatment-related liver transplant, or treatment-related hepatobiliary death. No patients receiving celecoxib or any nonselective NSAID met criteria for Hy's rule (alanine aminotransferase [ALT]  $\geq 3 \times$  upper limit of normal [ULN] with bilirubin  $\geq 2 \times$  ULN). The incidence of hepatic AEs in patients treated with celecoxib was similar to that for both placebo-treated patients and patients treated with ibuprofen or naproxen, but lower than for diclofenac.

*MO Comment. The study enrolled 2484 subjects on IBU 2400 mg/d and 4057 subjects on placebo. The results are reassuring. Authors affiliated with Pfizer.*

### **Cutaneous Drug Reactions**

**Raksha et al.** presented a case series of 200 cutaneous drug reactions from July 1997 to June 2006 in Vadodara, India. The most common drugs causing reactions were NSAIDs (42/200 or 21%). Ibuprofen was responsible for 20/200 (10%) of cases, and it was the commonest cause of erythema multiforme and Stevens Johnson syndrome in the study (3/6 Stevens Johnson cases were due to IBU).

*MO Comment. The OTC labeling for ibuprofen contains an allergy alert that warns consumers that if skin reddening, a rash, or blisters occur, they should stop use and seek medical attention.*

### **Bone**

**Alissa et al.** performed a randomized, placebo-controlled trial in 61 patients who received 132 dental implants, to investigate the effect of a one-week post-operative course of 600 mg of IBU taken four times a day on marginal bone level around dental implants. Two IBU patients did not complete the course because of stomach upset. There were no statistically significant differences between groups for mean marginal bone level change at 3 and 6 months.

*MO Comment. The Alissa et al. results do not pertain to OTC indications or use.*

*MO Comment. In summary there are risks of IBU at greater than OTC dose levels and durations: cardiovascular events MI's and stroke, GI ulceration and bleeding, and acute renal injury. There is general consistency of results from large observational studies in the UK, Denmark and US. The Agency believes the overall benefit versus risk profile for the non-prescription NSAIDs remains favorable when they are used according to the labeled directions. The incidence and severity of AEs are generally dose and duration of use dependent.*

*Serious cutaneous drug reactions are also well documented for IBU but occur uncommonly. Evidence from clinical trials continues to indicate that IBU taken concurrently with ASA inhibits the antiplatelet activity of ASA and may reduce its cardioprotective effect. All of these issues are already addressed in IBU labeling.*

*Also CHLOR can cause impaired driving ability which can occur without subjective drowsiness. The label has a warning to be careful when driving a motor vehicle or operating machinery. Labeling also warns that drowsiness may occur.*

- Alissa R, Sakka S, Oliver R, Horner K, Esposito M, Worthington HV, et al. Influence of ibuprofen on bone healing around dental implants: a randomized double-blind placebo-controlled clinical study. *Eur J Oral Implantol.* 2009;2(3):185-199.
- Banerji S, Anderson IB. Abuse of Coricidin HBP cough & cold tablets: episodes recorded by a poison center. *Am J Health Syst Pharm* 2001;19:1811-4.
- Catalano G, Catalano MC, Epstein MA, Tsambiras PE. OTc interval prolongation associated with citalopram overdose: A case report and literature review. *Clin Neuropharmacol* 2001 ;24: 158.(i2
- Danielsson BR, Lansdell K, Patmore L, Tomson T. Effects of the antiepileptic drugs lamotrigine, topiramate and gabapentin on hERG potassium currents. *Epilepsy Res* 2005;63: 17-25.
- Dutch MJ. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. *Med J Aust.* 2008 Jan 7;188(1):56-7.
- Farkouh ME, Verheugt FW, Ruland S, Kirshner H, Jeger R, Gitton X, et al. A comparison of the blood pressure changes of lumiracoxib with those of ibuprofen and naproxen. *J Clin Hypertens (Greenwich).* 2008 Aug;10(8):592-602.
- Fosbol EL, Gislason GH, Jacobsen S, Folke F, Hansen ML, Schramm TK, et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther.* 2009 Feb;85(2):190-7.
- Gengo FM, Rubin L, Robson M, Rainka M, Gengo MF, Mager DE, et al. Effects of ibuprofen on the magnitude and duration of aspirin's inhibition of platelet aggregation: clinical consequences in stroke prophylaxis. *J Clin Pharmacol.* 2008 Jan;48(1):117-22.
- Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbol EL, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Med.* 2009 Jan 26;169(2):141-9.
- Gladding PA, Webster MW, Farrell HB, Zeng IS, Park R, Ruijne N. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

- interaction with aspirin in healthy volunteers. *Am J Cardiol.* 2008 Apr 1;101(7):1060-3.
- Hawkey CJ, Weinstein WM, Stricker K, Murphy V, Richard D, Krammer G, et al. Clinical trial: comparison of the gastrointestinal safety of lumiracoxib with traditional nonselective nonsteroidal anti-inflammatory drugs early after the initiation of treatment--findings from the Therapeutic Arthritis Research and Gastrointestinal Event Trial. *Aliment Pharmacol Ther.* 2008 May;27(9):838-45.
- Hong HK, Jo SH (2009) Block of HERG k channel by classic histamine h(1) receptor antagonist chlorpheniramine. *Korean J Physiol Pharmacol* 13:215–220
- Hong Y, Gengo FM, Rainka MM, Bates VE, Mager DE. Population pharmacodynamic modelling of aspirin- and Ibuprofen-induced inhibition of platelet aggregation in healthy subjects. *Clin Pharmacokinet.* 2008;47(2):129-37.
- Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; 332: 1302–8.
- Lafrance JP, Miller DR. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. *Pharmacoepidemiol Drug Saf.* 2009 Oct;18(10):923-31
- Lamkin S, Fraiz A. An acid/base disturbance from ibuprofen toxicity. *J Emerg Nurs.* 2009 Nov;35(6):584-5
- Logan BK. Combined dextromethorphan and chlorpheniramine intoxication in impaired drivers. *J Forensic Sci.* 2009;54(5):1176-1180.
- McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; 296: 1633–44.
- Moore N. No obvious extra risk associated with low-dose NSAIDs. *Clin Pharm and Ther.* 2009, 86:602-604
- Murao S, Manabe H, Yamashita T, Sekikawa T. Intoxication with over-the-counter antitussive medication containing dihydrocodeine and chlorpheniramine causes generalized convulsion and mixed acidosis. *Inter Med* 2008;47:1013-1015.
- Nia AM, Fuhr U, Gassanov N, Erdmann E, Er F. Torsades de pointes tachycardia induced by common cold compound medication containing chlorpheniramine. *Eur J Clin Pharmacol.* 2010 Nov;66(11):1173-5.
- Prasad BM, Vijaya M, Reddy SB, Patil SR, Kalburgi NB. The effect of ibuprofen on bleeding during periodontal surgery. *Indian J Dent Res* 2008;19:22-5.
- Raksha MP, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. *Indian J Dermatol Venereol Leprol.* 2008 Jul-Aug;74(4):430.

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

- Renner B and K Brune. Are myocardial infarctions and death in healthy individuals associated with the use of cyclooxygenase inhibitors? *Clin Pharm and Ther.* 2009, 86:599-600.
- Roumie CL, Mitchel EF, Jr., Kaltenbach L, Arbogast PG, Gideon P, Griffin MR. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. *Stroke.* 2008 Jul;39(7):2037-45.
- Salata JJ, Jurkiewicz NK, Wallace AA, Stupienski RF 3rd, Guinasso PJ Jr, Lynch JJ Jr (1995) Cardiac electrophysiological actions of the histamine H1-receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. *Circ Res* 76:110–119
- Schneider V, Levesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure: A population-based, nested case control analysis. *Am J Epidemiol* 2006; 164: 881–889.
- Singh NP, Rizk JG. Oesophageal perforation following ingestion of over-the-counter ibuprofen capsules. *J Laryngol Otol.* 2008 Aug;122(8):864-6.
- Soni P, Shell B, Cawkwell G, Li C, Ma H. The hepatic safety and tolerability of the cyclooxygenase-2 selective NSAID celecoxib: pooled analysis of 41 randomized controlled trials. *Curr Med Res Opin.* 2009 Aug;25(8):1841-51.
- Tashiro M, Sakurada Y, Mochizuki H, Horikawa E, Maruyama M, Okamura N, et al. Effects of a sedative antihistamine, D-chlorpheniramine, on regional cerebral perfusion and performance during simulated car driving. *Hum Psychopharmacol.* 2008 Mar;23(2):139-50.
- Theunissen EL, Vermeeren A, Ramaekers JG. Repeated-dose effects of mequitazine, cetirizine and dexchlorpheniramine on driving and psychomotor performance. *Br J Clin Pharmacol* 2006;61(1):79–86.
- Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger P, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086
- Van Staa TP, Rietbrock S, Setakis E, Leufkens HG. Does the varied use of NSAIDs explain the differences in the risk of myocardial infarction? *J Intern Med.* 2008 Nov;264(5):481-92.
- Varas-Lorenzo C, Castellsague J, Stang MR, Perez-Gutthann S, Aguado J, Rodriguez LA. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. *Pharmacoepidemiol Drug Saf.* 2009 Nov;18(11):1016-25.
- Venkatraman N, O'Neil D, Hall AP. Life-threatening overdose with lamotrigine, citalopram, and chlorpheniramine. *J Postgrad Med.* 2008 Oct-Dec;54(4):316-7.

Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

Vermeeren A, Ramaekers JG, Van Leeuwen CJ, O'Hanlon JF. Residual effects on actual car driving of evening dosing of chlorpheniramine 8 and 12 mg when used with terfenadine 60 mg in the morning. *Human Psychopharmacol* 1998;13:S79–86.

## 9.2 Labeling Recommendations

In the complete response to the NA letter (see section 2.5), Pfizer proposed label changes to incorporate the labeling comments and to comply with the Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use Organ-Specific Warning Final Rule published in the April 29, 2009 Federal Register. Pfizer also revised the Uses section of the Drug Facts and the Principal Display Panel to add uses recognized in the 21 CFR 341.80(b)(2)(ii) and (iii), as with Advil Congestion Relief NDA 22-565. Additionally, based on comments received for NDA 22-565 on May 17, 2010, the following direction statement was added: “children under 12 years of age: do not use because this product contains too much medication for children under this age”.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



Clinical Review

Linda Hu

NDA 22-113

Advil Allergy & Congestion Relief: ibuprofen, phenylephrine, chlorpheniramine

---

### **9.3 Advisory Committee Meeting**

NA

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

/s/  
-----

LINDA S HU  
11/17/2011

DAIVA SHETTY  
11/18/2011

## Summary basis for Regulatory Action

<b>Date</b>	7/25/08
<b>From</b>	Joel Schiffenbauer
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	22-113
<b>Supp #</b>	
<b>Proprietary / Established (USAN) Names</b>	(b) (4) Chlorpheniramine, ibuprofen, phenylephrine
<b>Dosage Forms / Strength</b>	caplet
<b>Proposed Indication(s)</b>	Relief of symptoms associated with hay fever or other respiratory allergies, or the common cold
<b>Action:</b>	<i>Not Approvable</i>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Linda Hu/Steven Osborne
Statistical Review	
Pharmacology Toxicology Review	Wafa Harrouk
CMC Review/OBP Review	Bogdan Kurtyka
Microbiology Review	
Clinical Pharmacology Review	Partha Roy
DDMAC	
DSI	J. O'Shaughnessy
CDTL Review	Bindi Nikhar
OSE/DMETS	
OSE/DDRE	
OSE/DSRCS	
Other (labeling)	

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

## 1. Introduction to Review

The applicant, Wyeth Consumer Healthcare has submitted NDA 22,113 as a 505(b)(2) application for their over-the-counter (OTC) combination drug product, [REDACTED] (b) (4)

[REDACTED] This product contains three active ingredients, phenylephrine (PE) HCl 10 mg, ibuprofen (IBU) 200 mg and chlorpheniramine (CHLOR) maleate 4 mg. The proposed indications are the temporary relief of symptoms associated with hay fever, upper respiratory allergies and the common cold and the proposed dose in adults and children 12 years of age and older is 1 caplet every 4 to 6 hours while symptoms persist.

The sponsor currently markets a similar OTC combination drug product that contains pseudoephedrine instead of phenylephrine.

## 2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Ibuprofen (IBU) was first approved for prescription use in 1969, and for OTC use in the US in 1984 (NDA 18-989) and since then has become widely used for the temporary relief of minor aches and pain and reduction of fever. In the US alone, approximately 13 billion adult doses (200 mg) of ibuprofen were sold in 2004. Chlorpheniramine (CHLOR) is a first generation antihistamine, (H<sub>1</sub> receptor antagonist) that has been available for more than 40 years as an OTC antihistamine for relief of allergic rhinitis symptoms. Phenylephrine (PE) is a sympathomimetic amine with GRASE status as a decongestant in the monograph entitled Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (21 CFR 341.20). PE has been available for use as an OTC nasal decongestant since the early 1960s. PE (10 mg) was incorporated in this new product to replace pseudoephedrine HCl (30 mg) that is included in the currently marketed OTC product, Advil Allergy Sinus (NDA 22-441).

At a Pre-IND meeting with the sponsor on May 10, 2005, it had been discussed that if monograph doses of monograph ingredients were used in the reformulated drug product, a single, pivotal bioequivalence (BE) study would be adequate to support approval. The dose of chlorpheniramine would need to be adjusted from 2 mg in the original product to 4 mg in the new product in accordance with the monograph.

The applicant does not market a combination product containing ibuprofen, chlorpheniramine, and phenylephrine HCl anywhere in the world. Additionally the applicant states that the proposed combination is not marketed commercially anywhere by a different Sponsor.

### 3. CMC/Microbiology/Device

Following completion of the pivotal BE study, # AD-05-05, the final to-be-marketed (TBM) formulation was changed to include an antioxidant preservative (b) (4) propyl gallate (PG) (b) (4) the degradant, (b) (4) has since been qualified per ICH guidelines and is not considered a toxicological concern at the proposed levels.

At a Pre-NDA meeting with the sponsor on 3/19/2007, it was discussed that *in-vitro* dissolution data for the optimized product (containing the antioxidant PG) could be provided in support of a waiver of bridging *in-vivo* bioequivalence data between the original (non-PG) and optimized (PG) formulations. The proposed dissolution criteria (b) (4) in 30 minutes) have been determined to be adequate by Dr. Kurtyka.

In addition, per Dr. Kurtyka, several degradation products/impurities were identified during the drug development program for (b) (4). Among the degradants identified the only one of ongoing concern is (b) (4) a degradant (b) (4). Based on toxicological and statistical assessments of this degradant, a specification of NMT (no more than) (b) (4) relative to PE HCl has been proposed by the applicant for the post-approval stability program. Also see under the toxicology section 4 for a further discussion of the qualifying program for this degradant.

Therefore, the CMC reviewer concludes the following: *all chemical, physical, dissolution and microbiological stability data for the PG formulation were within specifications at all time points and storage conditions tested. The NDA has provided sufficient information to assure the identity, strength, purity and quality of (b) (4) over the proposed shelf life (18 months) when stored as labeled; labeling has been found acceptable.*

The CMC reviewer has recommended an Approvable action until the facilities involved are fully in compliance with cGMP requirements to assure identity, strength, purity and quality of the drug. The sponsor has committed to a post-approval stability program, which has been determined to be adequate.

For additional details, please refer to the CMC review by Dr. Bogdan Kurtyka.

### 4. Nonclinical Pharmacology/Toxicology

The toxicology review focused on the multiple degradants that were noted for this product. Propyl gallate a GRAS ingredient (listed under “substances added directly to human food” per 21 CFR 184.1660), was added (b) (4)

An additional degradant was identified in stability samples of the PG formulation to

be above the allowed level of 0.5% impurity relative to PE based on the ICH Q3B guidance determination. This degradant was (b) (4)

To qualify this degradant the applicant performed a 14-day general toxicity study as well as two genotoxicity studies. No evidence of genotoxicity was seen in the Ames test for (b) (4).

Oral dosing of (b) (4) for two weeks in Sprague-Dawley rats caused no significant toxicity. The MTD (maximum tolerated dose) and NOAEL (no observed adverse effect level) were greater than (b) (4) in Sprague Dawley rats. However, the stability data for the (b) (4) used in the general toxicity study, fell outside the sponsor's accepted range at 2-8°C on days 5 & 7, thus making the data for this treatment group questionable since the formulations were prepared weekly for this study.

Dr. Harrouk provides the following conclusions (taken from her review):

*The sponsor chose to conduct the shortest toxicology duration as per ICH Q3B qualification guidance (14 days general toxicity). The sponsor should have conducted the maximum duration of 90 days specified by the ICH Q3B given the potential exposure to this drug to treat allergy symptoms for a chronic duration. There was no evidence of toxicity or genotoxicity with mixtures of ibuprofen, phenylephrine HCl and chlorpheniramine maleate with up to (b) (4) when used for a period of 2 weeks. The (b) (4) degradant is considered qualified at concentration up to (b) (4) in the drug product. A 90-day toxicology study for the qualification of degradant (b) (4) needs to be conducted if the product were to be approved for use longer than 2 weeks. The study should use sufficiently high levels of the degradant (b) (4) that can be analytically confirmed.*

I agree with Dr. Harrouk. The clinical indication for this product (treatment of allergic symptoms) is one that is consistent with chronic use of the drug, and certainly more than 6 months over the lifetime of an individual. Therefore, I agree that a 90-day general toxicology study is appropriate. However, the applicant did not discuss this study with the division. They based the study length on previous acceptance of a qualifying study of 14 days by the Agency, albeit for a different indication (treatment of cold) for a different product.

Please refer to the Pharmtox review by Dr. Wafa Harrouk.

## **5. Clinical Pharmacology/Biopharmaceutics**

### **5.1. Notable issues**

The clinical pharmacology review addressed the single, pivotal bioequivalence study AD-05-05 conducted in support of NDA 22,113 and the DSI audit conducted at the sponsor's clinical and analytical lab sites that performed this study.

DSI conducted an audit of the clinical and analytical portions of the pivotal BE study (AD-05-05). (b) (4) conducted the analytical portions of the study. DSI concludes that the bioanalytical method for total phenylephrine is flawed and the reported subject sample concentrations are not accurate. This conclusion was based on the findings (b) (4) of incomplete hydrolysis of the PE-conjugates and instability of unconjugated PE under the conditions of hydrolysis. The inspection also found that the quality control samples used for the run acceptance were different from the subject samples, in that the quality controls were spiked with unconjugated PE only.

The analytical site lab (b) (4) apparently notified the sponsor (Wyeth) about the assay problems in July 2007; NDA 22,113 was however submitted on 9/25/2007 and neither the sponsor nor the lab informed the Agency about these issues. (b) (4) tried to revalidate the assay by randomly selecting samples from another Study # AD-06-06. Wyeth claimed that it is possible to extrapolate the outcome of the reanalysis for Study AD-06-06 to other studies that used the flawed method and that this is justified.

DSI and clinical pharmacology commented on the claim made by (b) (4) and Wyeth, that the degree of total PE concentration underestimation within a batch of samples processed together was consistent (i.e., that with-in batch samples underwent similar levels of hydrolysis), is not supported by the repeat data from Study AD-06-06. Specifically, they commented that the difference in original and repeat results between samples within a subject was highly variable and thus does not demonstrate a similar level of underestimation within a batch. Repeat results differed from the original concentrations by anywhere from 100-4300%, with many differences ranging from 150-300%. In their view, extrapolating the results of reanalysis of a subset of subject samples from Study AD-06-06 to Study AD-05-05 and other Wyeth studies that were analyzed using the flawed original method is not justified. I agree with this assessment.

The reader is referred to the review by Dr. O'Shaughnessy for details of the DSI evaluation.

A Clinical Pharmacology Office level briefing for NDA 22-113 was held subsequently and the conclusions were that NDA 22-113 is not acceptable because the PK data for PE are not reliable. The recommendation by Dr. Roy was that either a re-analysis of the stored PK samples be performed, or that a new PK study be performed using the TBM-formulation and the updated analytical methodology (see next).

**Study AD-05-05 (addressed by clinical pharmacology):**

This was a single-dose, 3-way, crossover, food/formulation effect bioavailability study conducted with the original (non-PG) formulation of IBU/PE/CHLOR. It compared the combination caplet IBU 200mg + PE 10 mg + CHLOR 4 mg (fasted and fed) to the reference products, Motrin IB tablet (IBU 200 mg), Sudafed PE tablet (10 mg) and Chlor-Trimeton Allergy tablet (CHLOR 4mg), all single ingredient products administered concomitantly in the fasted state. Forty-one subjects (19 males and 22 females) were enrolled; 40 completed all 3 treatment periods. However, the analytical assay for PE was found unacceptable based on a DSI inspection as discussed below (see section 12).

**Ibuprofen and Chlorpheniramine PK data:**

There was no formulation or food effect for IBU and CHLOR; the 90% confidence intervals for all key PK parameters fell within the 80-125% limits for bioequivalence. There was no effect of PE/CHLOR on AUC or Cmax of IBU compared to historical PK data.

However, compared to historical single ingredient ibuprofen PK data, PE appeared to delay Tmax of IBU by ~ 0.6 hour in males. Also, the addition of CHLOR to IBU and PE delayed the Tmax of IBU resulting in a potentially clinically significant delay of 1 hour (2.25 hr vs. 1.26 hr) between the triple combination caplet and historical ibuprofen (Nuprin®) data.

Based on the above Dr. Roy comments that the PK data for phenylephrine is flawed. He recommends that the applicant either re-analyze the stored PK samples provided stability for these samples can be assured, or analyze newly acquired PK samples (new BE study), using a validated analytical method for free PE. In regards to ibuprofen, he recommends that further analysis is needed to assess the impact of delayed Tmax of ibuprofen in the presence of phenylephrine and chlorpheniramine on clinical efficacy.

**6. Clinical Microbiology**

Not relevant for this product.

**7. Clinical/Statistical****7.1. General Discussion**

No efficacy studies were submitted with this application as PE is being substituted for PSE. Phenylephrine and chlorpheniramine are GRASE and can be found in 21 CFR 341. Ibuprofen has a history of extensive use.

**7.2. Efficacy**

No efficacy studies were submitted. The only clinical study was a PK study.

**7.3. Safety****7.3.1. Safety findings from submitted trials**

All three ingredients in the proposed fixed-combination drug product, [REDACTED] (b) (4) i.e. phenylephrine (PE), chlorpheniramine (CHLOR) and ibuprofen (IBU) have a long marketing history for OTC use, IBU since 1984, PE since the early 1960s and CHLOR for more than 40 years.

**Safety database - for NDA 22,113** was derived from a combined review of adverse event (AE) databases, literature and the PK Study # AD-05-05.

Study AD-05-05:

Fifteen out of the 40 subjects completing the study reported 21 AEs; the most common AEs included headache, followed by dizziness and dyspnea. The majority (19) of the AEs were rated as mild and the majority (19) were considered related to study medication; there was no placebo comparator. Per Dr. Osborne, AEs during the trial were consistent with the known AE profile of IBU, PE and CHLOR; no single AE occurred at a rate more than 2% in either treatment group. There were no clinically significant differences in subgroups of age, gender and race and no serious AEs or deaths were reported during the study.

### 7.3.2. Post-marketing safety

AE databases:

Adverse event data was reviewed from the AERS database (4/1/2001 to 3/31/2006) and the sponsor's safety database (4/30/2001 to 8/15/2006). The 4-month safety update submitted on 1/25/2008 included AERS data (4/1/2006 to 6/30/2007) and sponsor's AE data (8/16/2006 to 9/30/2007). Both databases included cases where an IBU, PHE and a CHLOR-containing product had been reportedly used. Currently, a combination product containing all three ingredients is not marketed worldwide.

Fifty one spontaneous AE cases, documenting exposure to all 3 ingredients were reported from the 2 databases (8 from sponsor's database and 43 from AERS). Of these 51 cases, 32 (1 sponsor case and 31 AERS cases), i.e. 63% were assigned to the Suspect cohort; this cohort was the primary data source for safety profile modeling and included cases where IBU, PHE and CHLOR containing products were designated as the suspect drugs. No deaths were reported in the suspect case cohort. In all 32 cases, a phenylpropanolamine (PPA) containing product was mentioned as a suspect drug. PPA, a nasal decongestant, was used in cough and cold preparations, and was withdrawn from the OTC marketplace.

Of the 31 AERS cases, 23 were listed as Serious; the single suspect case in the sponsor series was also included in these 23 cases. Since a PPA containing product was listed as a suspect drug for all cases in the Suspect cohort, the reported AEs and outcomes are confounded with respect to the contribution of IBU, PE and CHLOR to the reported events/outcomes. (See Dr. Osborne's review). No inferences about the safety of the proposed combination can be drawn based on these reports. Some of the AEs described above appear to be in keeping with the known AE profile of PPA (hypertension, stroke/cardiovascular accident, etc.).

The 4-month safety update included 5 cases where the 3 ingredients were described as being simultaneously ingested in the same patient; 3 from AERS and 2 from the sponsor database. One sponsor case was described as a SAE; AEs included somnolence, drug ineffective and incorrect dose administration.

**Literature Review:**

A literature search performed by the sponsor to assess AEs associated with use of IBU+PE+CHLOR from 1950 to 2007 did not reveal any safety concerns regarding their combined use.

**Safety Conclusions:**

Overall, the combined safety assessment for NDA 22,113 showed that the most common adverse events noted were in keeping with the known adverse event profile of IBU, PE and CHLOR. The available safety database was limited however, because the proposed new fixed-dose combination drug product has never been marketed worldwide before. In addition, safety conclusions from the BE study are based on a small number of patients (41) who participated in the study. Also, while the proposed combination drug product is similar to NDA 22,441, the decongestant is not identical (phenylephrine has replaced pseudoephedrine), and the dose of chlorpheniramine is 4 mg in the proposed new product as opposed to 2 mg in the old product. Finally, the majority of the SAEs in the post-marketing databases were confounded by the concomitant presence of phenylpropanolamine (PPA), which is considered unsafe for OTC use and has been withdrawn from the OTC marketplace.

It can be expected that common AEs for the proposed new combination drug product are likely to be non-serious and in keeping with the known AE profile of each of the three drugs, and furthermore, are also likely to not be different from the original triple combination containing pseudoephedrine, to any clinically meaningful extent, since PSE and PE are similar ingredients in the same drug class with similar safety concerns.

The proposed label conveys the cardiovascular risk warnings and the asthma warnings (associated with ibuprofen) which is appropriate. The label will have to limit duration of use for 7 days in keeping with the monograph limit of duration of use for phenylephrine.

Please refer to the Clinical NDA review by Drs. Steven Osborne and Linda Hu for additional details.

**8. Advisory Committee Meeting**

No Advisory Committee meeting was held for this submission. There was no new indication, no significant new safety issues, and the ingredients are either previously well studied (ibuprofen), or appear in a monograph as GRASE (phenylephrine).

However, a Citizen's Petition was submitted, questioning the efficacy of 10 mg phenylephrine as a decongestant and recommending higher doses. This issue was discussed in the Nonprescription Drug Advisory Committee (NDAC) meeting in December, 2007. The NDAC recommended that the 10 mg phenylephrine dose remain on the market for use in adults, given evidence of efficacy for the 10 mg dose. For details of the NDAC meeting the reader is referred to the transcripts for the meeting.

## 9. Other Regulatory Issues

### 9.1. Pediatrics

The applicant is requesting a waiver of pediatric studies for children less than 12 years of age. At this time, studies may be waived for children less than 2 years of age based on safety concerns (discussed extensively at the Advisory committee meeting on cough and cold products and use in children, held October 2007). For children 2 to less than 12 years of age, there is no regulatory reason to waive studies. This product is likely to be used in children of this age. The applicant should be asked to develop an age appropriate formulation for this product for children down to 2 years of age. It is unclear at this time as to whether studies are needed for children 12 to less than 17 years of age since the monograph would allow dosing down to 12, but PREA defines the pediatric population as up to 18.

Dr. Hari Sachs (from the pediatric group) provided a consult response and the reader is referred to her consult for additional discussion of pediatric issues related to this product. She provided the following comments:

*Pediatric studies in children 2 to 12 could be deferred if the product was approved down to age 12, in which case studies in adolescents could be required as a post-marketing commitment, taking into account existing monograph information regarding these ingredients. If it was approved for adults only, pediatric studies could be deferred for patients 2 to 17 years and a pediatric plan would have to be submitted by the sponsor. Partial waiver for children < 2 maybe granted and labeling must reflect safety concerns in this age group. Age appropriate formulations must be developed by the sponsor.*

## 10. Financial Disclosure

No issues were identified.

## 11. Labeling

Based on results of the DSI audit and clinical pharmacology reviews and issues related to the phenylephrine assays and because the product will not be approved this review cycle, no labeling discussions took place. However, there are 2 points regarding labeling that will be addressed here.

First, the applicant requested that an additional warning be added regarding the exacerbation of asthma with the use of NSAID containing products. A review of the prescription labels for NSAIDs including ibuprofen reveals that the Medication Guides describe “asthma attacks in people who have asthma” as a serious side effect. Based on this and the literature that the applicant provided, it is reasonable to include “asthma” under the section “ask your doctor if you have...” See also Dr. Hu’s review of the literature provided by the applicant in support of

adding this information to the OTC label. Furthermore, this warning is now being added to other OTC NSAID products.

Second, the amount of phenylephrine (10 mg) in each tablet exceeds monograph dosing for children < 12 years of age. The applicant requested that the label for this product state that the product should not be used by children under the age of 12. I agree with this recommendation. However, PREA is triggered and the applicant will need to develop an age appropriate formulation (see section 9) if this product is eventually approved.

In addition, in keeping with the monograph duration of use for PE which is 7 days, the use of (b) (4) caplets should be limited to 7 days: (b) (4).

## 12. DSI Audits

See section 5 above for a discussion of the results of the DSI audit.

## 13. Conclusions and Recommendations

### 13.1. Regulatory action

Based on the DSI inspection and recommendations from the clinical pharmacology group, I recommend that this NDA not be approved and that the sponsor repeat the PK studies using the new phenylephrine assay. It is further recommended that the applicant include an ibuprofen comparator because the comparison to historical controls demonstrates that the T<sub>max</sub> is delayed.

In addition, the applicant should be requested to perform another qualifying general toxicity study for the degradant (b) (4) for 2 reasons. First, the original study was only 14 days in duration. The indication for this product is one in which consumers will potentially use this product on a chronic basis. Therefore, rather than accepting the shortest duration for a qualifying study of 14 days, the applicant should be required to obtain pre-clinical data that address the potential for long term use of the product. Second, there were concerns expressed by Dr. Harrouk that the (b) (4) used in the general toxicity study was not stable, and thus animals actually received less (b) (4) than the estimated dose. Therefore, data for the treatment group in the general toxicity study may not be reliable. For both of these reasons, the applicant should be required to repeat the general toxicity study for 90 days, and ensure that the (b) (4) used is stable and that animals receive an accurately determined dose.

In terms of safety, the human safety data provided did not raise any new signals of concern.

Finally, it should also be noted that the chlorpheniramine was increased from 2 mg in the product containing PSE, to 4 mg in this product to conform to dosing recommendations in the monograph for the ingredient CHLOR.

### 13.1.1. Important issues (*resolved or outstanding*)

If the product is eventually approved, the labeling changes should be made to change the duration of use to 7 days and add the asthma warning.

Inspection of one facility was found to be unacceptable.

### 13.1.2. Required studies (*PREA; Subpart E/H/I approvals*)

PREA is triggered by this application. If approved the applicant will need to develop an age appropriate formulation down to 2 years. It is unclear at this time as to whether studies are needed for children 12 to less than 17 years of age.

## 13.2. Comments to be conveyed to the applicant

The following comments should be conveyed to the applicant:

The submitted PK data for phenylephrine are unreliable due to major flaws in the analytical assay methodology. Further, any differences noted between the original and repeat results between samples within a subject, was highly variable and did not demonstrate a similar level of underestimation within a batch. Therefore, we do not believe that extrapolating the results of reanalysis of a subset of subject samples from Study AD-06-06 to Study AQ-05-05, that were analyzed using the flawed original method, is justified.

A cross-study comparison of ibuprofen PK data from your proposed triple combination caplet (Study AD-05-05) to the historical ibuprofen PK data suggested that the mean  $T_{max}$  values of ibuprofen increased approximately 1 hr in the presence of phenylephrine and chlorpheniramine. Further analysis is needed to assess the potential impact of delayed  $T_{max}$  of IBU from your proposed product on clinical efficacy.

Therefore, you should submit pharmacokinetic data for phenylephrine using an adequately validated analytical assay method. With advances in analytical method for free phenylephrine, we recommend that you develop a sensitive assay for quantifying unmetabolized (free) phenylephrine in the plasma samples. You should analyze newly acquired phenylephrine PK samples. We recommend that you also include ibuprofen (single ingredient) in any new PK study that you perform. The repeat BE study should include the to-be-marketed formulation.

Alternatively you may select to reanalyze the stored PK samples from your previous PK study AQ-05-05 for phenylephrine, provided stability of these samples can be assured. However, you will still need to address the  $T_{max}$  changes for ibuprofen.

In addition, we note that the qualifying study for the (b) (4) degradant was 14 days in duration. However, the indication for this product, treatment of allergy symptoms is such that chronic use is likely to occur. Therefore, you will need to perform a qualifying study of maximum duration of 90 days as specified by the ICH Q3B given the potential exposure of

this drug to treat allergy symptoms for a chronic duration. The study should use sufficiently high levels of the degradant (b) (4) that can be analytically confirmed.

You should submit any new protocols for our review.

In regards to labeling, the label should convey a 7 day limit for duration of use ((b) (4)) in keeping with the monograph dosing for phenylephrine. The inclusion of the asthma warnings and the 'do not use in less than 12 years' are appropriate and should be included in updated labeling.

One of the facilities involved in your submission is deemed not to comply with cGMP requirements. Satisfactory resolution of any deficiencies of the facility is required to assure identity, strength, purity and quality of the drug product.

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

/s/

-----  
Joel Schiffenbauer  
7/25/2008 11:00:00 AM  
MEDICAL OFFICER

**Cross-Discipline Team Leader Review**  
**NDA # 22,113** (b) (4)

<b>Date</b>	5/30/2008
<b>From</b>	Bindi Nikhar, MD
<b>Subject</b>	Cross-Discipline Team Leader Memo
<b>NDA#</b>	22,113
<b>Applicant</b>	Wyeth Consumer Healthcare
<b>Date of Submission</b>	9/25/2007
<b>PDUFA Goal Date</b>	7/25/2008
<b>Proprietary Name/ Established (USAN) names</b>	(b) (4)
<b>Dosage forms/Strength</b>	Ibuprofen 200mg, Phenylephrine HCl 10 mg, Chlorpheniramine maleate 4 mg
<b>Proposed Indication(s)</b>	Temporary relieves symptoms associated with hay fever or other upper respiratory allergies and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, fever.
<b>Recommended</b>	Not Approvable

## 1. Introduction

The sponsor, Wyeth Consumer Healthcare has submitted NDA 22,113 as a 505(b)(2) application for their over-the-counter (OTC) combination drug product, (b) (4). This product contains three active ingredients, phenylephrine (PE) HCl 10 mg, ibuprofen (IBU) 200 mg and chlorpheniramine (CHLOR) maleate 4 mg. The sponsor currently markets a similar OTC combination drug product that contains pseudoephedrine instead of phenylephrine. The proposed indications are the temporary relief of symptoms associate with hay fever, upper respiratory allergies and the common cold and the proposed dose in adults and children 12 years and older is 1 caplet every 4 to 6 hours while symptoms persist. A pediatric waiver has been requested for age groups 0 to 12 years.

The sponsor conducted one pivotal bioequivalence study (Study AD-05-05) in support of their 505(b)(2) application. On DSI inspection of the sponsor's analytical and clinical lab sites in March 2008, it was revealed that there were major flaws in the analytical assay that quantifies the total PE (unmetabolized PE plus PE converted back from conjugated PE metabolites). Assay method problems included incomplete hydrolysis of conjugated PE metabolites, PE instability in the buffer used and lack of appropriate quality controls. Based on this flawed assay, results from the pivotal bioequivalence study cannot be considered acceptable to support approval of NDA 22,113.

## 2. Background

21 CFR 341.40 (c) permits the combination of a monograph antihistamine (eg., chlorpheniramine) + monograph oral nasal decongestant (eg., phenylephrine) + any generally recognized safe and effective single analgesic-antipyretic active ingredient. The incorporation of ibuprofen in [REDACTED] <sup>(b) (4)</sup> that is not included in the monograph required the submission of a NDA for this triple ingredient combination.

IBU is a non-steroidal, anti-inflammatory drug (NSAID) that was approved for prescription use in 1969 and for OTC use in the UK in 1983 and in the US in 1984. In keeping with other NSAIDs, it has analgesic, antipyretic and anti-inflammatory properties, by reducing prostaglandin (PG) biosynthesis.

PE is a sympathomimetic amine that has been available as an OTC nasal decongestant since the early 1960s. It is included as a safe and effective (Category 1) oral nasal decongestant in the final monograph of Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for OTC use (21 CFR 341.20). It acts predominantly by a direct action on  $\alpha$ -adrenergic receptors; in therapeutic doses, it does not have a stimulant effect on the  $\beta$ -adrenergic receptors of the heart ( $\beta_1$ ), and bronchi or peripheral blood vessels ( $\beta_2$ ).

CHLOR is a first generation antihistamine, ( $H_1$  receptor antagonist) that has been available for more than 40 years as an OTC antihistamine for relief of allergic rhinitis symptoms. It is included as a safe and effective (Category 1) antihistamine in the final monograph of Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for OTC use (21 CFR 341.12).

### Combat Methamphetamine Act (2005)

Phenylephrine HCl (10 mg) was incorporated in this new product to replace pseudoephedrine HCl (30 mg) that is included in the currently marketed OTC product, Advil Allergy Sinus, NDA 22,441. The pseudoephedrine product was moved 'behind the counter' in compliance with the Combat Methamphetamine Epidemic Act of 2005 that restricted the sale of all pseudoephedrine containing drug products over the counter.

At a Pre-IND meeting with the sponsor on May 10 2005, it had been discussed that if monograph doses of monograph ingredients were used in the reformulated drug product, a single, pivotal bioequivalence (BE) study that compared the new formulation with the three individual ingredients in fed and fasted states would be adequate to support approval. The dose of chlorpheniramine would need to be adjusted from 2 mg in the original product to 4 mg in the new product in accordance with the monograph. No new clinical safety and efficacy studies would be required if bioequivalence was shown between the old and new products. In response, the sponsor conducted a single BE study, # AD-05-05 in support of NDA 22,113 that is discussed later.

### 3. CMC

(b) (4) contains the following drug substances- Ibuprofen, Phenylepinephrine HCl and Chlorpheniramine maleate. Per the CMC reviewer, all the drug master files are adequate to support this NDA and all drug substances are described in corresponding USP monographs, with Phenylepinephrine and Chlorpheniramine being in the final OTC monograph. Issues discussed briefly include formulation change, degradants and expiration dates.

#### Formulation change:

Following completion of the pivotal BE study, # AD-05-05, the final to-be-marketed (TBM) formulation was changed to include an antioxidant preservative (b) (4) propyl gallate (PG) (b) (4). Based on accelerated stability data, this degradant was predicted to rise above ICH threshold levels (0.5%) by the end of the 18 month shelf life period. The degradant, (b) (4) has since been qualified per ICH guidelines and is not considered a toxicological concern at the proposed levels.

At a Pre-NDA meeting with the sponsor on 3/19/2007, it was discussed that *in-vitro* dissolution data for the optimized product (containing the antioxidant PG) could be provided in support of a waiver of bridging *in-vivo* bioequivalence data between the original (non-PG) and optimized (PG) formulations {21 CFR 320.22 (d)(4)}. The sponsor was asked to follow the SUPAC guidance section III.B.2 case C for selection of the multiple dissolution media for their *in vitro* dissolution profile comparison. Per the CMC reviewer, the proposed dissolution criteria (b) (4) in 30 minutes) have been found to be adequate. The sponsor conducted a bridging BE study (AD-06-06) between the original and optimized formulations; data from this study have however not been submitted to NDA 22,113.

#### Degradants:

Per the CMC reviewer, several degradation products/impurities were identified during the drug development program for (b) (4) as follows:

IBU – All IBU related impurities and degradant results were less than the applicable reporting limits at all time points and storage conditions tested.

PHE – All PHE related impurities and degradants were less than the applicable specifications at all time points and storage conditions tested. However, 3 new PE degradants, (b) (4), discussed earlier were identified during the stability study:

(b) (4)

CHLOR – All CHLOR maleate related impurities and degradants were less than reporting limits at all time points and storage conditions, except the (b) (4). Per the CMC reviewer, based on a safety assessment of this degradant and the extensive history of safe use of CHLOR maleate in OTC products, a limit of NMT (b) (4) is proposed for (b) (4) for the post-approval stability program.

Expiration dates:

Based on stability data for the drug product, the sponsor has proposed an expiration period of 18 months for (b) (4) when stored at 20-25<sup>0</sup> C in blisters or pouches and a (b) (4) bulk storage time. The 18 month expiration date has been found to be acceptable; however the (b) (4) bulk storage time has been found unacceptable and the sponsor has agreed to a bulk holding time (b) (4). Per the CMC review, the levels of degradants at (b) (4) and trends in their increase assure that their levels at the proposed expiration will still be below specification limits.

CMC Conclusions:

Per the CMC reviewer, all chemical, physical, dissolution and microbiological stability data for the PG formulation were within specifications at all time points and storage conditions tested. The NDA has provided sufficient information to assure the identity, strength, purity and quality of (b) (4) over the proposed shelf life (18 months) when stored as labeled; labeling has been found acceptable.

The CMC reviewer has recommended an Approvable action from the CMC perspective pending satisfactory completion of cGMP inspections. The sponsor has committed to a post-approval stability program, which has been determined to be adequate.

Please refer to the CMC review by Dr. Bogdan Kurtyka.

#### **4. Non-clinical Pharmacology/Toxicology**

The Pharmtox review for the reformulated (b) (4) caplet revolved mainly around the PE degradants.

As discussed earlier, the original formulation of (b) (4) had been shown to produce an oxidized degradant of PE, (b) (4). Per the Pharmtox reviewer, during the qualification program, the sponsor identified a positive mutagenicity signal for the Ames assay and reformulated the product to include the antioxidant preservative, propyl gallate (PG). Propyl gallate a GRAS ingredient, listed under “substances added directly to human food” per 21 CFR 184.1660 was added (b) (4)

Two additional degradants were identified in stability samples of the PG formulation to be above the allowed level of 0.5% impurity relative to PE based on the ICH Q3B guidance determination. These were IBU (b) (4)

Both these degradants underwent a qualification program that consisted of two genotoxicity studies and one general toxicity study. No evidence of genotoxicity was seen in the Ames test for both (b) (4) and no evidence of toxicity was seen in the general toxicity studies for both. The (b) (4) degradant is considered qualified at concentrations up to (b) (4)

#### **Pharmtox Conclusions:**

The Pharmtox reviewer has concluded that there are no non-clinical safety issues relevant to clinical use and has recommended an approvable action for NDA 22,113. There are no post-marketing commitments.

Please refer to the Pharmtox review by Dr. Wafa Harrouk.

## **5. Clinical Pharmacology/Biopharmaceutics**

The Biopharm review revolved around the single, pivotal bioequivalence study AD-05-05 conducted in support of NDA 22,113 and the DSI audit conducted at the sponsor's clinical and analytical lab sites that performed this study.

#### **Study AD-05-05:**

This was a single-dose, 3-way, crossover, food/formulation effect bioavailability study conducted with the original (non-PG) formulation of IBU/PE/CHLOR. It compared the combination caplet IBU 200mg + PE 10 mg + CHLOR 4 mg (fasted and fed) to the reference products, Motrin IB tablet (IBU 200 mg), Sudafed PE tablet (10 mg) and Chlor-Trimeton Allergy tablet (CHLOR 4mg), all single ingredient products administered concomitantly in the fasted state. 41 subjects (19 males and 22 females) were enrolled; 40 completed all 3 treatment periods. One subject voluntarily withdrew due to difficulty in blood draws.

#### **Phenylepinephrine PK data:**

The analytical assay for PE was found unacceptable based on a DSI inspection as discussed below. Total PE (unmetabolized *plus* PE converted from conjugated PE by adding  $\beta$ -glucuronidase) was measured in the assay. PE undergoes extensive metabolism following oral dosing to PE sulfate and PE glucuronide and other Phase 1 metabolites. The exposure to unmetabolized (free) PE is in the low ng/ml range, hence historically, total PE is measured for PK assessment. Relative contributions of PE and its conjugated metabolites to efficacy are not clear.

DSI Audit (by Dr. Jacqueline O'Shaughnessy)

A lab site (b) (4) inspection was conducted by the Division of Scientific Regulations (DSI) for the clinical (3/4-3/6/2008) and analytical (3/11-3/14/2008) portions of this study. The audit reported major flaws identified in the analytical assays that quantify the total phenylepinephrine (PE) values.

Reported flaws with the assay (Assay V2) were as follows:

- Incomplete hydrolysis of conjugated PE metabolites; incubation time was not optimal
- PE was unstable in buffer used; pH was too high (PE oxidized)
- PE was used as quality control; no commercially available PE glucuronide and sulfate at time of sample analysis and lack of control for hydrolysis process

The inspection concluded that the PE data were inaccurate and resulted in an overall underestimation of total PE and there was a lack of reproducibility. Per the report, the original results were significantly underestimated compared to the repeat results, with differences ranging from 100-4300%.

The analytical site lab (b) (4) apparently notified the sponsor (Wyeth) about the assay problems in July 2007; NDA 22,113 was however submitted on 9/25/2007 and neither the sponsor nor the lab informed the Agency about these issues. (b) (4) tried to revalidate the assay (Assay V3), randomly selected samples from a new BE Study, # AD-05-06 (that compared the original non-PG and optimized PG formulations) and reanalyzed them; this confirmed that the old assay had showed lower concentrations. Study AD-05-06 has not been submitted to the Agency for review.

The sponsor's assessment is that the BE findings for NDA 22,113 are valid, even with a flawed assay method. They state that all samples (all treatments and all time points) for individual subjects were assayed in the same batch run; that replicate samples from sample re-assays demonstrated intra-batch reproducibility; that lack of reproducibility of repeat PK samples was related to inter-batch variability caused by incomplete hydrolysis of PE conjugates; and that AUCL and Cmax from plasma concentrations by either method V2 or V3 produced comparable findings of bioequivalence in a subset of subjects from Study AD-05-06.

The biopharm reviewers have concluded that (a) extrapolating outcome of reanalysis for Study AD-05-06 to other studies that used the flawed method is not justified and (b) the sponsor claim that the degree of total PE underestimation within a batch of samples processed together was consistent (i.e. within batch samples underwent similar levels of hydrolysis) is not supported by repeat data from AD-05-06. The difference in original and repeats between samples was highly variable and the data did not demonstrate a similar level of underestimation within a batch.

From the Clin-Pharm perspective, NDA 22, 113 is not acceptable because the PK data for Phenylepinephrine were unreliable. The biopharm reviewer has recommended two

options to resolve the PE analysis issues: a). reanalysis of the stored PK samples from AD-05-05 using an adequately validated analytical method for PE *or* b). conduct an entirely new PK study identical in design to AD-05-05 using the to-be-marketed caplet formulation of IBU/PE/CHLOR and analyze the new PK data for PE using an adequately validated analytical method for PE.

Ibuprofen and Chlorpheniramine PK data:

There was no formulation or food effect for IBU and CHLOR; the 90% confidence intervals for all key PK parameters fell within the 80-125% limits for bioequivalence. There was no effect of PE/CHLOR on AUC or Cmax of IBU compared to historical PK data.

However, compared to historical single ingredient ibuprofen PK data, PE appeared to delay Tmax of IBU by ~ 0.6 hour in males. Also, the addition of CHLOR to IBU and PE delayed the Tmax of IBU resulting in a significant delay of 1 hour (2.25 hr vs. 1.26 hr) between the triple combination caplet and historical ibuprofen (Nuprin®) data. This would imply that ~ 50% less subjects would have IBU concentrations above EC50 at earlier time-points (≤ 1 hour). Per the Biopharm review, both in-house analyses as well as literature data suggest that for both analgesic and antipyretic PK/PD models of ibuprofen, the EC50 is in the range of 6-10 µg/ml. This delayed IBU Tmax in the presence of PE/CHLOR is likely to be of clinical significance for (b) (4) that is indicated as a combination *analgesic/antipyretic/nasal decongestant/antihistamine* drug product. Per the Biopharm reviewer, if the PK program were to be repeated, it is recommended that the new PK study should have an IBU only treatment arm for within-study comparisons.

**Cross-study comparison of IBU plasma concentrations at 30 min and 60 min in subjects receiving IBU/PE/CHLOR caplet (NDA 22,113) and Nuprin® (IBU alone from NDA 20-135, historical data) under fasted state**

	NDA 22-113 (this submission)		NDA 20-135 (historical)	
	30 min	60 min	30 min	60 min
<b>% of subjects ≥ 6 µg/mL</b>	45 (18/40)	70 (28/40)	77 (17/22)	92 (22/24)
<b>% of subjects ≥ 10 µg/mL</b>	27.5 (11/40)	42.5 (17/40)	55 (12/22)	86 (19/24)
<b>Mean (µg/mL)</b>	7.3	10.1	13.8	16.3
<b>SD (µg/mL)</b>	5.2	6.9	9.7	6.7
<b>CV%</b>	71.8	68.0	33.8	29.0

Source: Biopharm review for NDA 22-113 by Dr. Partha Roy

**Biopharm Conclusions:**

Based on DSI findings, phenylepinephrine data from Study AD-05-05 cannot be considered reliable for exposure and bioequivalence determination for NDA 22,113. The sponsor could either conduct a reanalysis of the stored PK samples from AD-05-05 (may be difficult given the age of the samples) using an adequately validated analytical method

*or* conduct an entirely new PK study using a study design identical to AD-05-05, using the to-be-marketed formulation of [REDACTED] (b) (4). The delayed Tmax for ibuprofen of almost an hour in the presence of chlorpheniramine and phenylephrine is likely to be of clinical significance and will have to be addressed.

Please refer to the Biopharm review by Dr. Partha Roy and the DSI report by Dr. Jacqueline O'Shaughnessy.

## **6. Clinical Microbiology**

Not applicable. No new microbiology studies were done for this application. Per the CMC reviewer, all microbiological stability data for the PG formulation [REDACTED] (b) (4) were within specifications at all time points and storage conditions tested.

## **7. Clinical/Statistical – Efficacy**

No new clinical efficacy and safety studies were conducted for NDA 22,113, [REDACTED] (b) (4) a combination product containing phenylephrine 10 mg + ibuprofen 200 mg + chlorpheniramine 4 mg. The sponsor currently markets a product containing ibuprofen 200 mg + pseudoephedrine HCl 30 mg + chlorpheniramine maleate 2 mg as pain reliever/fever reducer, nasal decongestant and antihistamine under the trade name Advil Allergy Sinus caplets (NDA 21,441, approved on December 12, 2002), which is sold behind the counter. This is in compliance with The Combat Methamphetamine Epidemic Act of 2005, which legislated that all pseudoephedrine (PSE) containing drug products be moved behind the counter. NDA 22,113 is expected to offer a pseudoephedrine-free option in the OTC market.

The proposed indications are 'temporary relief of symptoms associated with hay fever or other upper respiratory allergies and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, fever'. The proposed dose in adults and children 12 years and older is one caplet every 4 hours (maximum of 6 caplets in a 24 hour period).

For NDA 21,441, the triple combination caplet had been tested in a single clinical efficacy and safety trial at both the one-tablet (IBU/PSE/CHLOR=200mg/30mg/2mg) and 2-tablet (IBU/PSE/CHLOR=400mg/60mg/4mg) doses in patients 12 years and older with seasonal allergic rhinitis. While both doses were efficacious, there were no statistically significant differences between both doses in any of the efficacy parameters. Doubling the dose led to an increase in dose-related adverse events associated with the three individual ingredients. Given this risk-benefit ratio, the lower dose combination tablet was approved for OTC use.

A Pre-IND meeting was held on 5/10/2005 to discuss development plans for the proposed phenylephrine containing products in response to the new legislation. At the meeting,

the sponsor was informed that if recognized monograph doses of monograph ingredients were to be used in their proposed new drug product, then a pharmacokinetic approach would be acceptable; clinical studies would be required if the PK studies did not demonstrate bioequivalence. Appropriate monograph doses were chosen for PE and CHLOR for NDA 22,133 in the >12 years age group and the sponsor conducted a single bioequivalence study, # AD-05-05 which was the pivotal study for this NDA.

**Efficacy conclusions:** As discussed in Section 5, the pivotal PK/BE study, # AD-05-05 for NDA 22,113 was found to have a flawed method for assaying phenylepinephrine. Based on this, PK data from this study are unreliable and NDA 22,113 is not likely to be approved. In addition, the study also showed that the IBU Tmax was delayed by about 1 hour in the presence of PE/CHLOR. This is likely to be of clinical significance for (b) (4) that is indicated as a combination *analgesic/antipyretic/nasal decongestant/antihistamine* drug product.

Please refer to the Clinical review by Dr. Steven Osborne and follow-up memo by Dr. Linda Hu (Dr. Osborne left the division in March, 2008 and the NDA was re-assigned to Dr. Hu).

## 8. Safety

All three ingredients in the proposed fixed-combination drug product, (b) (4) i.e. phenylepinephrine (PE), chlorpheniramine (CHLOR) and ibuprofen (IBU) have a long marketing history for OTC use; IBU since 1984, PE since the early 1960s and CHLOR for more than 40 years.

Ibuprofen (IBU)- AEs associated with ibuprofen, an NSAID, are dose and duration dependent and in general, the severity and frequency of AEs is expected to be less with OTC than Rx use. Most common AEs involve the GI tract (eg., nausea, abdominal pain, dyspepsia, heartburn); serious AEs such as peptic ulcer and GI bleeding events can also occur. Other AEs include headache, dizziness, nervousness, renal events, rash, etc.; more recently, NSAIDs have been known to be associated with cardiovascular (CV) risks. The CV risk associated with OTC ibuprofen use is thought to be small and the proposed label for (b) (4) has the cardiovascular risk warning, which is in keeping with all OTC NSAID labels. Ibuprofen has been known to cause a severe allergic reaction, especially in people allergic to aspirin and current OTC NSAID labels include the Allergy Alert warning. This warning however does not mention that ibuprofen use may be associated with NSAID-associated asthma. Severe asthmatics are at a greater risk for NSAID-induced asthma and the Rx label for ibuprofen conveys this risk. The sponsor has proposed updating the (b) (4) label to include the asthma risk, which is appropriate.

Phenylepinephrine (PE) – is a sympathomimetic drug, included in the final monograph (21 CFR 341.80) as a nasal decongestant. AEs associated with PE use include nervousness, restlessness, anxiety, dizziness, tremor, etc. and it should be used with

caution in patients with hypertension, diabetes mellitus, ischemic heart disease and prostatic hypertrophy.

Chlorpheniramine (CHLOR) – is a first generation antihistamine included in the final monograph (21 CFR 341.72) as an anti-allergy drug. AEs associated with CHLOR use include somnolence, lassitude, dizziness and incoordination. It may also be associated with a paradoxical stimulation of the CNS, especially in pediatric age groups. Other AEs include headache, psychomotor impairment, antimuscarinic effects and GI effects such as nausea, vomiting and diarrhea.

**Safety database - for NDA 22,113** was derived from a combined review of adverse event (AE) databases, literature and the PK Study # AD-05-05.

AE databases:

Adverse event data was reviewed from the AERS database (4/1/2001 to 3/31/2006) and the sponsor's safety database (4/30/2001 to 8/15/2006). The 4 month safety update submitted on 1/25/2008 included AERS data (4/1/2006 to 6/30/2007) and sponsor data (8/16/2006 to 9/30/2007). Both databases included cases where an IBU, PHE and a CHLOR-containing product had been reportedly used. Currently, a combination product containing all three ingredients is not marketed worldwide.

51 spontaneous AE cases, documenting exposure to all 3 ingredients were reported from the 2 databases (8 from sponsor's database and 43 from AERS). Of these 51 cases, 32 (1 sponsor case and 31 AERS cases), i.e. 63% were assigned to the Suspect cohort; this cohort was the primary data source for safety profile modeling and included cases where IBU, PHE and CHLOR containing products were designated as the suspect drugs. No deaths were reported in the suspect case cohort. In all 32 cases, a phenylpropanolamine (PPA) containing product was mentioned as a suspect drug. PPA, a nasal decongestant was used in cough and cold preparations, it is now considered unsafe for OTC use due to its proposed association with hemorrhagic stroke, and is being withdrawn from the OTC marketplace.

Serious AEs (SAEs) - Of the 31 AERS cases, 23 were listed as Serious; the single suspect case in the sponsor series was also included in these 23 cases; these are described briefly below.

- Sponsor SAE - This included hemorrhagic stroke, seizures, atrial arrhythmia, vasospasm and severe elevation of blood pressure in a patient who had a history of polysubstance abuse and bipolar disorder and had taken multiple Rx and OTC medications.

- AERS SAEs – These included cardiac disorders (angina, coronary artery disease, myocardial infarction, sinus tachycardia, etc), GI disorders (dyspepsia, hematemesis, melena, peptic ulcer, etc), asthenia, chest pain, lab abnormalities (decreased chloride, sodium and increased glucose), neoplasms (breast cancer, malignant lymphoid neoplasm), nervous system disorders (cerebellar & cerebral infarction, cerebrovascular accident, convulsion, encephalopathy, lacunar infarction, etc), psychiatric disorders (anxiety, decreased activity, mental disorder), respiratory disorders (dyspnea, aspiration

pneumonia), vascular disorders (deep vein thrombosis, hypertension, etc.). The most common serious AEs based on MedDRA preferred coding terms included Injury (26 mentions) and Cerebrovascular Accident (8 mentions).

Since a PPA containing product was listed as a suspect drug for all cases in the Suspect cohort the reported AEs and outcomes are confounded with respect to the contribution of IBU, PE and CHLOR to the reported events/outcomes. (See Dr. Osborne's review). No inferences about the safety of the proposed combination can be drawn based on these reports. Some of the AEs described above appear to be in keeping with the known AE profile of PPA (hypertension, stroke/cardiovascular accident, etc.).

The 4 month safety update included 5 cases where the 3 ingredients were described as being simultaneously ingested in the same patient; 3 from AERS and 2 from the sponsor database. One sponsor case was described as a SAE; AEs included somnolence, drug ineffective and incorrect dose administration.

#### Study AD-05-05:

15 out of the 40 subjects completing the study reported 21 AEs; most common AEs included headache, followed by dizziness and dyspnea. Majority (19) of the AEs were rated as mild and the majority (19) were considered related to study medication; there was no placebo comparator. Per Dr. Osborne, AEs during the trial were consistent with the known AE profile of IBU, PE and CHLOR; no single AE occurred at a rate more than 2% in either treatment group. There were no clinically significant differences in subgroups of age, gender and race and no serious AEs or deaths were reported during the study.

#### Literature Review:

A literature search performed by the sponsor to assess AEs associated with use of IBU+PE+CHLOR from 1950 to 2007 did not reveal any safety concerns regarding their combined use.

#### **Safety Conclusions:**

Overall, the combined safety assessment for NDA 22,113 showed that the most common adverse events noted were in keeping with the known adverse event profile of IBU, PE and CHLO. The available safety database was limited however, because the proposed new fixed-dose combination drug product has never been marketed worldwide before and the sponsor's and AERS safety databases were presumptive in that the three drugs were used concomitantly. In addition, safety conclusions from the BE study are based on a small number of patients (41) who participated in the study. Also, while the proposed combination drug product is similar to NDA 22,441, the decongestant is not identical (phenylephrine has replaced pseudoephedrine), and the dose of chlorpheniramine is 4 mg in the proposed new product as opposed to 2 mg in the old product.

The majority of the SAEs in the post-marketing databases were confounded by the concomitant presence of phenylpropanolamine (PPA), which is considered unsafe for OTC use and has been withdrawn from the OTC marketplace.

Although a clear determination of safety for NDA 22,113 cannot be drawn based on available data, it can be expected that common AEs for the proposed new combination drug product are likely to be non-serious and in keeping with the known AE profile of each of the three drugs.

The proposed label conveys the cardiovascular risk warnings and the asthma warnings (associated with ibuprofen) which is appropriate. The label will have to limit duration of use for 7 days in keeping with the monograph limit of duration of use for phenylephrine.

Study AD-05-05 showed that the ibuprofen T<sub>max</sub> was delayed in the presence of chlorpheniramine and phenylephrine by almost one hour. There does not appear to be a potential for drug abuse or overdose.

Please refer to the Clinical NDA review by Dr. Steven Osborne.

## **9. Advisory Committee Meeting**

A combined Nonprescription and Pediatric Advisory Committee (AC) meeting was held on October 18 and 19, 2007 to discuss the use of cough and cold drugs in pediatric age groups in response to a Citizen Petition; the focus was primarily on the 0 to 6 years age groups. It was discussed that there was overall inadequate safety and efficacy data regarding the use of these products in pediatric age groups, in particular, the youngest age groups. The need for adequate PK data and the need for clinical safety and efficacy studies and/or the feasibility of extrapolation from reasonably well conducted studies in adults was discussed. The AC recommended that due to safety concerns, cough and cold products should not be used below 2 years of age either as single ingredients or in combination and recommended obtaining PK, safety and efficacy data for cough and cold products in the 2 to 6 years age groups. The Committee did not address use of cough and cold products in the 6 to 12 years age groups. Recommendations from this meeting are currently being deliberated within the Agency and are likely to impact drug development programs for cough and cold products, primarily in pediatric age groups.

In addition, a Nonprescription AC meeting was held on December 14, 2007 in response to a Citizen Petition to discuss the efficacy of the current monograph dose of phenylephrine (10 mg) in cough and cold products. Adult age groups were primarily discussed and pediatric age groups were not discussed at this meeting. The Committee concluded that in adults, there is evidence suggestive that the 10 mg dose is likely to be effective in controlling symptoms of the common cold, but further studies, including PK, PD and clinical studies would be helpful, and that it would also be useful to study the safety and effectiveness of higher doses of phenylephrine. The Sponsor's formulation incorporates the maximum single dose (10 mg) and 24-hour (60 mg) adult dose of phenylephrine.

## 10. Pediatrics

(b) (4) is indicated for adults and children 12 years and older and the proposed dose is one caplet every 4 hours (maximum of 6 caplets in a 24 hour period) for the temporary relief of hay fever, other respiratory allergies, and the common cold. The proposed doses exceed the approved OTC doses for both IBU and PE in children < 12 years of age. At initial NDA submission, the proposed label had indicated that children less than 12 years of age could consult a doctor; however, in a labeling supplement (1/31/2008) the sponsor has re-proposed that the product not be used in children under 12 years of age, which is acceptable.

The sponsor has proposed a full pediatric waiver for the 0 to less than 12 years age groups, indicating that (b) (4) does not represent a meaningful therapeutic benefit over existing treatments, that it may not be used in a substantial number of children, that the dose of IBU and PE exceed the recommended doses for children < 12 years of age and that children may have difficulty swallowing pills.

Although the sponsor gives the above reasons for a waiver, the indications for (b) (4), i.e. common colds and allergies are frequently seen in children. In addition, combination products may be perceived as being simpler to use in pediatric age groups and may be preferred over single ingredient drug products. NDA 22,113 triggers PREA (Pediatric Research and Equity Act), and PREA mandates that age-appropriate formulations be developed for pediatric age groups; the sponsor will have to address these issues during their drug development program.

Thus, a full pediatric waiver would not apply for NDA 22,113; a partial waiver in the 0 to 2 years age group would be appropriate given safety reasons as discussed at the AC meeting in October, 2007.

The sponsor will be expected to provide PK, safety and efficacy data for the new proposed combination in the 2 to 12 years age group. It is unclear if extrapolation of efficacy in this age group from well-conducted studies in adolescents and adults is possible, i.e. if it can be reasonably assumed that children when compared to adults would have a similar response to intervention. It was discussed at the AC meeting in October 2007 that for drugs indicated for allergic rhinitis, efficacy in pediatric age groups can be reasonably extrapolated from well conducted clinical studies in adults. This was based on the allergic rhinitis disease model, where the course of the disease and response to intervention are expected to be similar across both age groups. (b) (4) is however indicated for both the cough and cold *and* allergic rhinitis indications; also, there are no adequate and well-controlled studies of the phenylephrine and ibuprofen combination products in adolescents and adults to extrapolate from; hence, PK, efficacy and safety studies would be required in this age group.

Clinical data (PK, safety and efficacy) would also be required for the 12 to 17 years age groups since extrapolation of efficacy is not possible, given the lack of well-conducted clinical studies in adults. However, while PREA necessitates studies in this age range, the

monograph allows dosing down to 12 years. At the present time, deliberations are ongoing within the Agency regarding the need for clinical studies in the 12 to 17 years pediatric age groups.

*Pediatric consult (by Dr. Hari Sachs):*

*A Pediatrics consult was obtained for NDA 22,113 regarding the need for pediatric studies. The consult concluded that pediatric studies are required under PREA for (b) (4) [redacted]. Pediatric studies in children 2 to 12 could be deferred if the product was approved down to age 12, in which case studies in adolescents could be required as a post-marketing commitment, taking into account existing monograph information regarding these ingredients. If it was approved for adults only, pediatric studies could be deferred for patients 2 to 17 years and a pediatric plan would have to be submitted by the sponsor. Partial waiver for children < 2 maybe granted and labeling must reflect safety concerns in this age group. Age appropriate formulations must be developed by the sponsor.*

Please refer to the Pediatrics consult by Dr. Hari Sachs.

## **11. Other Relevant Regulatory Issues**

- Certification of no financial interests has been supplied; there were no financial disclosures. (b) (6) (b) (4) [redacted]
- Patent information has been provided for (b) (4) [redacted] caplet; active ingredients being IBU 200mg, PE HCl 10 mg and CHLOR maleate 4 mg
- A DSI audit performed for the clinical and analytical portions of the pivotal bioequivalence study, # A-05-05 in March 2008, revealed major flaws in the analytical portions of the study for phenylephrine. This has been discussed in Section 5 (Clin Pharm); based on this assay, PK results for NDA 22,113 are unreliable and NDA 22,113 is not likely to be approved
- A Pediatric consult was obtained to discuss the need for pediatric studies for NDA 22,113; this has been discussed in Section 10 (Pediatrics). Discussions regarding PREA versus monograph regulations for requirement of PK and clinical studies in 12 to 17 years age group are ongoing within the Agency

## **12. Labeling**

The proposed labeling for (b) (4) [redacted] caplets was generally in keeping with similar OTC products and was appropriate. In an amendment dated 1/31/2008, the sponsor made the following labeling proposals:

- Include asthma warning (Ask a doctor before use if you have asthma).

(b) (4) [redacted]

The asthma risk is based on the known risk of asthma associated with IBU/NSAID use (sponsor provided literature references – please see Dr. Steve Osborne’s review), is present in current NSAID prescription labels and is appropriate. Due to lack of adequate PK, efficacy and safety data in pediatric age groups it is appropriate for the label to convey that these caplets should not be used in children < 12 years of age.

In addition, in keeping with the monograph duration of use for PE which is 7 days, the use of (b) (4) caplets should be limited to 7 days; this will need to be conveyed to the sponsor.

All these amendments should be included in the updated label upon approval of this NDA.

### 13. Recommendations/Risk Benefit Assessment

It is recommended that NDA 22,113 not be approved based on the DSI audit (March, 2008) that reported major flaws in the assays for phenylepinephrine in the pivotal BE study, # AD-05-05. PK data results for phenylepinephrine from this BE study are unreliable to support approval of NDA 22,113. The sponsor has two options to resolve the PE analysis issues: **a).**reanalysis of the stored PK samples from AD-05-05 using an adequately validated analytical method for PE *or* **b).**conduct an entirely new PK study identical in design to AD-05-05 using the to-be-marketed caplet formulation of IBU/PE/CHLOR and analyze the new PK data for PE using an adequately validated analytical method for PE.

This delayed ibuprofen Tmax (almost one hour) in the presence of PE/CHLOR in Study AD-05-05 is likely to be of clinical significance for (b) (4) that is indicated as a combination *analgesic/antipyretic/nasal decongestant/antihistamine* drug product and will have to be addressed. Per the Biopharm reviewer, if the PK program were to be repeated, it is recommended that the new PK study have an IBU only treatment arm for within-study comparisons.

Although a combination drug product can be advantageous, a potential risk with such fixed-drug combinations is the inadvertent intake of ingredient(s) no longer needed as symptoms resolve. Another risk is that of misuse and overdose, especially when combined with other OTC cough, cold and allergy products that contain similar ingredients. Such risks could be of particular concern if this product was to be taken for longer than 7 days, which is feasible for allergic rhinitis symptoms. Safety related issues regarding the use of combination drug products for cough and cold indications were discussed at the AC meeting in October 2007. The overall risk-benefit profile (b) (4) is likely to be favorable under labeled OTC conditions, once appropriate PK, safety and efficacy data are available for all age groups and PREA issues have been addressed. Potential risks outlined above could be addressed via appropriate labeling.

**Recommendations for sponsor:**

- 1). The sponsor could either conduct a reanalysis of the stored PK samples from AD-05-05 using an adequately validated analytical method for PE *or* conduct an entirely new PK study identical in design to AD-05-05 using the to-be-marketed caplet formulation of IBU/PE/CHLOR and analyze the new PK data for PE using an adequately validated analytical method for PE.
  
- 2). Delayed ibuprofen Tmax (almost one hour) in the presence of phenylephrine/chlorpheniramine in Study AD-05-05 is likely to be of clinical significance for [REDACTED] <sup>(b) (4)</sup> that is indicated as a combination *analgesic/antipyretic/nasal decongestant/antihistamine* drug product. If the PK program were to be repeated, it is recommended that the new PK study have an IBU only treatment arm for within-study comparisons.
  
- 3). PREA is triggered by NDA 22,113; the sponsor will have to address pediatric age groups during their drug development program. If this NDA is approved, age – appropriate formulations will need to be developed down to 2 years of age. The need for PK and clinical studies in the 12 to 17 years age group is being discussed within the Agency.
  
- 4). Labeling would have to convey a 7 day limit for duration of use [REDACTED] <sup>(b) (4)</sup> in keeping with the monograph dosing for phenylephrine.
  
- 5). The inclusion of the asthma warnings and the ‘do not use in less than 12 years’ are appropriate and should be included in updated labeling.

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

/s/

-----  
Bindi Nikhar

6/2/2008 12:48:20 PM

MEDICAL OFFICER

Non-approvable based on flawed pivotal bioequivalence study.



**DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service**

Division of Nonprescription Products (DNCE),  
Center for Drug Evaluation and Research

**MEMORANDUM**

Application Type	NDA
Submission Number	22-113
Letter Date	September 25, 2007
Stamp Date	October 1, 2007
Reviewer Name	Linda Hu, M.D.
Team Leader	Bindi Nikhar, M.D.
Established Name	ibuprofen (200 mg), phenylephrine (10mg), chlorpheniramine (4 mg)
(Proposed) Trade Name	(b) (4)
Therapeutic Class	analgesic/antipyretic decongestant antihistamine
Applicant	Wyeth Consumer Healthcare
Formulation	caplet
Dosing Regimen	Adults and children 12 years and older: take 1 caplet, every 4 hours while symptoms persist. Do not take more than 6 caplets in 24 hours, unless directed by a doctor.
Indication	For the temporary relief of the following symptoms associated with hay fever or other respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, and fever.
Intended Population	adults and children 12 years of age and older

## **Recommendation on Regulatory Action**

Approval for OTC marketing is not recommended for (b) (4) since a flawed phenylephrine assay was used in the pivotal PK study, thereby making the results unreliable and non-reproducible. The proposed indication, for adults and children aged 12 and above, is “temporarily relieves these symptoms associated with hay fever or other respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, and fever.”

This memo is an addendum to the review of this NDA by Dr. Steve Osborne (dfs'd 3/14/08), who has moved to another division. Dr. Osborne concluded that the proposed combination of ibuprofen 200 mg/phenylephrine 10 mg/chlorpheniramine 4 mg (b) (4) has an acceptable safety profile based on marketing experience and literature. While the particular combination has not been marketed before, the individual ingredients have been marketed for a significant time and extent as an NDA product (ibuprofen) or a monograph product (phenylephrine and chlorpheniramine).

The Biopharm, Chemistry, and Pharmtox reviews were not completed at the time of Dr. Osborne's departure (nor are they finalized as of this writing). The Sponsor requested a full waiver of pediatric studies for this drug product, but PREA has been triggered by this application. The Agency has concerns regarding the safety and efficacy of cold/cough products when used in the pediatric population as discussed at the October 2007 Nonprescription Drug Advisory Committee meeting. The Advisory Committee recommended assessing the clinical safety and efficacy and the pharmacokinetics of these products in the pediatric population.

Other outstanding issues at the time of Dr. Osborne's review include: the biopharmaceutics reviewer's assessment of the bioequivalence study #AD-05-05, the chemistry reviewer's assessment of the dissolution study linking the current formulation with the formulation used in study #AD-05-05, the status of the phenylephrine degradant (b) (4), and the pharmacology-toxicology reviewer's assessment of the rat toxicology study of the other phenylephrine degradant, (b) (4).

### **4.1 Chemistry Manufacturing and Controls**

The original formulation used in the PK study did not contain propyl gallate (PG). During development of the product, several degradation products were noted. The original submission states that all of these degradants fell below the ICH qualification limit of 0.5% of the pharmaceutically active material except for (b) (4), levels of which may exceed the ICH qualification guidance limit through the shelf life of the product. During the qualification program, the Sponsor identified a positive mutagenicity signal for the Ames assay and decided to reformulate the product. Wyeth discovered that the addition of antioxidant propyl gallate (b) (4)

The Sponsor proposed to use comparative in vitro dissolution data in support of a waiver of an in vivo bioequivalence study between the 2 formulations (with and without PG). This approach was discussed with the Agency and approved. At the pre-NDA meeting on March 19, 2007, the Agency told the applicant that their request for a waiver of bioequivalence studies was “acceptable provided the in vitro dissolution profiles using multiple dissolution media are identical between the PG and non-PG products.” They were advised to follow the SUPAC guidance section III.B.2 case C for selection of the multiple dissolution media for the in vitro dissolution profile comparison.

Dissolution method #D7284 was utilized to perform the dissolution testing.

The samples evaluated were:

- [REDACTED] (b) (4) tablets, without PG (non-PG), WH-1232-0001-009 manufactured on 03-Feb-2006
- [REDACTED] (b) (4) tablets, with PG (PG), WH-1232-0006-003 manufactured on 02-Sep-2006

The dissolution curves were measured for 6 tablets in each solution. The data were collected according to the SUPAC guidance for High Permeability, Low Solubility Drugs. Multi-point dissolution profiles were performed in water, 0.1 N HCl, and USP media at pH 4.5, 6.5, and 7.5. Samples were collected at 15, 30, 45, 60, and 120 minutes until either 90% of drug from drug product is dissolved or an asymptote reached.

The CMC reviewer found the dissolution patterns of PG and non-PG formulations to be similar and evaluated the dissolution data to be acceptable and adequate for approval.

Three additional phenylephrine degradants were identified during the stability study and are discussed below. The trends observed in the stability studies indicate that other degradants and impurities will not reach ICH qualification limits during the proposed expiration period.



At this time two establishments are awaiting OC approval, but there are no other outstanding CMC issues. See Dr. Kurtyka's review for further details and analysis of results.

#### 4.3 Preclinical Pharmacology/Toxicology

(b) (4) underwent a qualification program consisting of two genotoxicity studies and one general toxicity study:

- Ames *Salmonella* histidine reversion assay
- Human lymphocyte chromosome aberration assay and
- 2-week general toxicity study in rats spiked with (b) (4)

For (b) (4), no evidence of genotoxicity was seen in the Ames *Salmonella* histidine reversion or the human chromosome aberration assays at concentrations of up to (b) (4) relative to phenylephrine. Similarly, no evidence of toxicity was seen in the general toxicity studies in rats at concentrations of up to (b) (4) relative to phenylephrine. Therefore, the pharmtox reviewer states that the (b) (4) degradant is considered qualified at concentrations up to concentrations of up to (b) (4).

See Dr. Harrouk's review for further details and analysis of results.

#### 4.4 Clinical Pharmacology

A single pharmacokinetic study was submitted in support of this NDA. Study AD-05-05 is a single-dose, three-way crossover, food/formulation effect bioavailability study with an earlier development formulation of IBU/PE/CHLOR. Following the completion of Study AD-05-05, the final to-be-marketed formulation was changed to include an antioxidant preservative ((b) (4) propyl gallate or "PG") (b) (4)

A site inspection was conducted by the Division of Scientific Investigations (DSI) for the clinical and analytical portions of the pivotal PK study, AD-05-05. Major flaws were identified in the analytical assay for total PE (unmetabolized PE plus PE converted back from conjugated PE metabolites). The assay method problems include incomplete hydrolysis of conjugated PE metabolites, PE instability in the hydrolysis buffer, and lack of appropriate quality controls. Based on the findings of the DSI inspection of this study,

Biopharm concludes that the PE data contained in Study AD-05-05 can no longer be considered acceptable based on the regulatory standards to support this NDA. (See DSI inspection report)

Biopharm reached this conclusion because the PK data for PE in the NDA submission were not reliable due to major flaws with the bioanalytical method at the (b) (4) analytical site identified by DSI. Biopharm recommends that in order to resolve the PE assay issue, the sponsor has two options: 1) reanalyze the stored PK samples from study AD-05-05 using an adequately validated analytical method for PE if the stability of these samples can be assured or 2) repeat the pivotal BE study with the to-be-marketed formulation of IBU/PE/CHLOR and analyze the newly acquired PE PK samples, using a validated analytical method for free PE.

Biopharm also noted that a cross-study comparison of ibuprofen PK data from Study AQ-05-05 to the historical ibuprofen PK data suggests that the mean  $T_{max}$  values of ibuprofen increased approximately 1 hour in the presence of phenylephrine and chlorpheniramine. The Sponsor should therefore address the potential impact of delayed  $T_{max}$  of ibuprofen from the proposed clinical product on clinical efficacy. Further, Biopharm recommended that the Sponsor include an ibuprofen (single ingredient) arm in any new PK study that is performed for this NDA.

This reviewer agrees that the PK data from Study AQ-05-05 are not acceptable because of the flawed analytical assay and that it would be preferable to include a single ingredient ibuprofen arm in any new PK study for this application. See Dr. Partha Roy's review for further details.

## **9.2 Labeling Recommendations**

The directions for use and the warnings for the individual ingredients, ibuprofen, phenylephrine, and chlorpheniramine, appear to be appropriate except for the following. The label should state a maximum of 7 days of use to be consistent with the monograph limit of 7 days of use for phenylephrine. Also, the label should include a "do not use" direction for children less than 12 years of age since the amount of phenylephrine (10 mg) and chlorpheniramine (4mg) exceeds monograph dosing for this age range. Finally, the reviewer agrees with the Sponsor's proposal to add an asthma warning.

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

/s/

-----  
Linda Hu  
5/30/2008 03:49:19 PM  
MEDICAL OFFICER

Bindi Nikhar  
5/30/2008 06:48:33 PM  
MEDICAL OFFICER

This memo by Dr. Linda Hu is in addition  
to the Clinical review by Dr. Steven Osborne.  
Agree with Nonapprovable action due to flawed pivotal  
bioequivalence study.

## CLINICAL REVIEW

Application Type	NDA 22-113
Submission Number	
Submission Code	
Letter Date	September 25, 2007
Stamp Date	October 1, 2007
PDUFA Goal Date	July 21, 2008
Reviewer Name	Steven F. Osborne, M.D.
Review Completion Date	March 12, 2008
Established Name	ibuprofen, phenylephrine, chlorpheniramine
(Proposed) Trade Name	 (b) (4)
Therapeutic Class	Pain reliever, antihistamine, decongestant
Applicant	Wyeth Consumer Healthcare
Priority Designation	S
Formulation	Caplet
Dosing Regimen	Adults and children 12 years and older: take 1 caplet, every 4 hours while symptoms persist. Do not take more than 6 caplets in 24 hours, unless directed by a doctor.

**Indication**

For the temporary relief of the following symptoms associated with hay fever or other respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, and fever.

**Intended Population**

Adults and children 12 years of age and older

## Table of Contents

<b>1 EXECUTIVE SUMMARY .....</b>	<b>6</b>
1.1 RECOMMENDATION ON REGULATORY ACTION.....	6
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS.....	6
1.2.1 Risk Management Activity .....	6
1.2.2 Required Phase 4 Commitments .....	6
1.2.3 Other Phase 4 Requests .....	7
1.3 SUMMARY OF CLINICAL FINDINGS .....	7
1.3.1 Brief Overview of Clinical Program.....	7
1.3.2 Efficacy.....	7
1.3.3 Safety.....	7
1.3.4 Dosing Regimen and Administration.....	8
1.3.5 Drug-Drug Interactions.....	8
1.3.6 Special Populations.....	8
<b>2 INTRODUCTION AND BACKGROUND .....</b>	<b>8</b>
2.1 PRODUCT INFORMATION.....	9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS .....	10
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES .....	10
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS .....	11
2.5 PRESUBMISSION REGULATORY ACTIVITY.....	11
2.6 OTHER RELEVANT BACKGROUND INFORMATION .....	11
<b>3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES .....</b>	<b>12</b>
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE).....	12
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY.....	12
<b>4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....</b>	<b>13</b>
4.1 SOURCES OF CLINICAL DATA .....	13
4.2 TABLES OF CLINICAL STUDIES .....	13
4.3 REVIEW STRATEGY.....	13
4.4 DATA QUALITY AND INTEGRITY.....	13
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES .....	13
4.6 FINANCIAL DISCLOSURES .....	14
<b>5 CLINICAL PHARMACOLOGY .....</b>	<b>14</b>
5.1 PHARMACOKINETICS .....	14
5.2 PHARMACODYNAMICS .....	18
5.3 EXPOSURE-RESPONSE RELATIONSHIPS.....	18
<b>6 INTEGRATED REVIEW OF EFFICACY .....</b>	<b>18</b>
6.1 INDICATION .....	18
6.1.1 Methods .....	18
6.1.2 General Discussion of Endpoints.....	19
6.1.3 Study Design.....	19
6.1.4 Efficacy Findings.....	19
6.1.5 Clinical Microbiology.....	19
6.1.6 Efficacy Conclusions .....	19
<b>7 INTEGRATED REVIEW OF SAFETY .....</b>	<b>19</b>
7.1 METHODS AND FINDINGS .....	19
7.1.1 Deaths .....	21

7.1.2 Other Serious Adverse Events .....	21
7.1.3 Dropouts and Other Significant Adverse Events .....	21
7.1.4 Other Search Strategies.....	22
7.1.5 Common Adverse Events .....	22
7.1.6 Less Common Adverse Events .....	25
7.1.7 Laboratory Findings.....	25
7.1.8 Vital Signs .....	26
7.1.9 Electrocardiograms (ECGs).....	26
7.1.10 Immunogenicity.....	26
7.1.11 Human Carcinogenicity .....	26
7.1.12 Special Safety Studies.....	27
7.1.13 Withdrawal Phenomena and/or Abuse Potential .....	27
7.1.14 Human Reproduction and Pregnancy Data.....	27
7.1.15 Assessment of Effect on Growth .....	27
7.1.16 Overdose Experience .....	27
7.1.17 Postmarketing Experience .....	28
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS .....	33
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety .....	33
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	34
7.2.3 Adequacy of Overall Clinical Experience .....	34
7.2.4 Adequacy of Special Animal and/or In Vitro Testing .....	34
7.2.5 Adequacy of Routine Clinical Testing.....	34
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup.....	34
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study .....	34
7.2.8 Assessment of Quality and Completeness of Data .....	35
7.2.9 Additional Submissions, Including Safety Update .....	35
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS .....	35
7.4 GENERAL METHODOLOGY.....	35
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence .....	35
7.4.2 Explorations for Predictive Factors .....	36
7.4.3 Causality Determination .....	36
<b>8 ADDITIONAL CLINICAL ISSUES .....</b>	<b>37</b>
8.1 DOSING REGIMEN AND ADMINISTRATION .....	37
8.2 DRUG-DRUG INTERACTIONS.....	37
8.3 SPECIAL POPULATIONS.....	37
8.4 PEDIATRICS .....	37
8.5 ADVISORY COMMITTEE MEETING .....	38
8.6 LITERATURE REVIEW .....	38
8.7 POSTMARKETING RISK MANAGEMENT PLAN .....	46
8.8 OTHER RELEVANT MATERIALS .....	46
<b>9 OVERALL ASSESSMENT.....</b>	<b>46</b>
9.1 CONCLUSIONS .....	46
9.2 RECOMMENDATION ON REGULATORY ACTION.....	46
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS.....	47
9.3.1 Risk Management Activity.....	47
9.3.2 Required Phase 4 Commitments.....	47
9.3.3 Other Phase 4 Requests .....	47
9.4 LABELING REVIEW .....	47
9.5 COMMENTS TO APPLICANT.....	50

Clinical Review  
Steven Osborne, M.D.  
{NDA 22-113}

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

---

<b>10 APPENDICES .....</b>	<b>50</b>
10.1 REVIEW OF INDIVIDUAL STUDY REPORTS .....	50
10.2 LINE-BY-LINE LABELING REVIEW .....	50
<b>REFERENCES .....</b>	<b>52</b>

## **1 EXECUTIVE SUMMARY**

This review reflects the available data and assessments of the data by this reviewer as of March 14, 2008. This reviewer is moving to another division within FDA. Any addendums to this review will be made by Linda Hu, M.D. from the Division of Nonprescription Clinical Evaluation.

### **1.1 RECOMMENDATION ON REGULATORY ACTION**

The proposed combination of ibuprofen 200 mg/phenylephrine 10 mg/chlorpheniramine 4 mg ( (b) (4) ) has an acceptable safety profile for OTC marketing; however, the final determination will be made upon complete review of outstanding Chemistry, Pharmtox, and Biopharm issues as discussed below. While the combination has not been marketed before, the individual ingredients have been marketed for a significant time and extent as an NDA product (ibuprofen) or monograph product (phenylephrine and chlorpheniramine). At the present time, it is unclear if the product can be approved for pediatric age groups (the sponsor is requesting approval for age groups 12 and above). Given the Advisory Committee meeting in October 2007 that discussed safety and efficacy of cough and cold products in the youngest pediatric age groups, discussions regarding extrapolation of efficacy from adult to pediatric age groups are ongoing within the Agency.

Other outstanding issues at this time that could impact approval of the product include: the biopharmaceutics reviewer's assessment of the bioequivalence study #AD-05-05, the chemistry reviewer's assessment of the dissolution study linking the current formulation with the formulation used in study #AD-05-05, the status of the phenylephrine degradant (b) (4) and the pharmacology-toxicology reviewer's assessment of the rat toxicology study with the degradant, (b) (4).

### **1.2 Recommendation on Postmarketing Actions**

At present, it is not clear whether the Sponsor will need to conduct any postmarketing actions for this product.

#### **1.2.1 Risk Management Activity**

No special post-marketing risk management activities are recommended.

#### **1.2.2 Required Phase 4 Commitments**

At present, it is not clear whether the Sponsor will need to conduct any Phase 4 studies for this product.

### 1.2.3 Other Phase 4 Requests

None, at this time.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Wyeth Consumer Healthcare (WCH) is seeking approval to market over-the-counter (OTC) a new combination drug product, (b) (4) caplets for adults and children over 12 years of age for the indication: for the temporary relief of the following symptoms associated with hay fever or other respiratory allergies and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, and fever.

(b) (4) contains 200mg ibuprofen, 10 mg phenylephrine, and 4 mg chlorpheniramine in a caplet dosage form. Phenylephrine has replaced pseudoephedrine in the previously approved Advil Allergy Sinus product, which is currently marketed behind-the-counter along with Children's Advil Allergy Sinus, due to the pseudoephedrine component.

### 1.3.2 Efficacy

One bioequivalence study (#AD-05-05) was submitted with this application in support of efficacy. This study was a randomized, single-dose, open-label, 3-way crossover food effect/formulation effect study in forty-one (41) subjects. Forty subjects completed the study. The findings were:

- Under fasted conditions, the (b) (4) caplet has an equivalent rate (Cmax) and extent (AUC) of absorption of ibuprofen, phenylephrine, and chlorpheniramine compared to the single entity products ibuprofen (Motrin IB), phenylephrine (Sudafed PE), and chlorpheniramine (Chlor-Trimeton Allergy).
- The Tmax for the phenylephrine component of (b) (4) caplet was delayed in the presence of food compared with the Tmax of Sudafed PE.

These data will be evaluated by the biopharmaceutics reviewer to determine if they satisfy the Agency criteria for bioequivalence and whether the delay in Tmax for phenylephrine in the presence of food is clinically significant. Any clinically significant food effect could be addressed in labeling, if needed.

### 1.3.3 Safety

The overall evaluation of safety for the (b) (4) caplet, containing ibuprofen 200 mg/ phenylephrine 10 mg/ chlorpheniramine 4 mg, included adverse event data from a single-dose

bioequivalence study (AD-05-05), a review of the Sponsor's adverse event database, data from the FDA AERS database, and a review of the literature.

There were no deaths or serious adverse events in study AD-05-05. Since the combination product has not been marketed before, a systematic review of AE databases showed no instances of use of the combination product. A search in which concomitant exposure to products that contain the 3 individual ingredients revealed 1 serious adverse event from the Sponsor's database and 23 serious adverse events from the AERS database. These cases did not raise new safety concerns for the individual ingredients ibuprofen, phenylephrine, or chlorpheniramine.

An additional literature search on ibuprofen alone revealed 54 references mostly discussing potential cardiovascular, central nervous system, gastrointestinal, central nervous system, allergy and renal adverse events. There were no new adverse events not previously reported for ibuprofen that were revealed in this literature review.

### **1.3.4 Dosing Regimen and Administration**

For adults and children 12 years and older: take 1 tablet every 4 hours, while symptoms persist. Do not take more than 6 caplets in 24 hours, unless directed by a doctor. The Sponsor notes that the product is intended for use for up to (b) (4) consecutive days for pain (ibuprofen component), up to 7 consecutive days for the treatment of nasal congestion (phenylephrine and chlorpheniramine components), and up to 3 consecutive days for the treatment of fever (ibuprofen component). Since the product is intended for use as an allergy and sinus condition reliever, the monograph limit of 7 days use of phenylephrine and chlorpheniramine will be applied to this product and require labeling for a maximum of 7 days use.

### **1.3.5 Drug-Drug Interactions**

The Sponsor's data on potential drug-drug interactions between the individual ingredients did not show any clinically meaningful interactions.

### **1.3.6 Special Populations**

The proposed labeling has all the appropriate warnings for consumers of certain age categories with underlying medical conditions, or for those people taking interacting medications. In particular there are do not use warnings for individuals right before or after heart surgery (cardiovascular risk) or if an individual is taking (or took within 2 weeks) a MAO inhibitor (accelerated hypertension risk).

## **2 Introduction and Background**

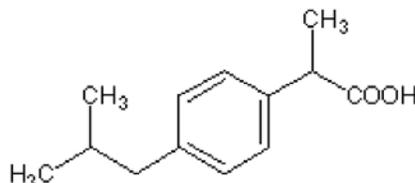
This is a clinical safety review of the pain reliever/decongestant/antihistamine combination product, (b) (4) caplet, filed under NDA 22-113. Phenylephrine has replaced pseudoephedrine in the previously approved Advil Allergy Sinus product.

## 2.1 Product Information

The combination of the over-the-counter (OTC) analgesic, ibuprofen, with the nasal decongestant, pseudoephedrine hydrochloride (pseudoephedrine), and the antihistamine, chlorpheniramine maleate (chlorpheniramine), was approved as a solid oral dosage form on December 12, 2002 (NDA 21-441). Subsequent to approval, pseudoephedrine-containing products were moved behind the counter in conformance with The Combat Methamphetamine Epidemic Act of 2005. WCH is now submitting the new drug product, with phenylephrine HCl 10 mg substituted for pseudoephedrine as the nasal decongestant, under the trade name (b) (4)

The level of chlorpheniramine has also been adjusted from 2 mg to 4 mg, to reflect the appropriate dose required in the monograph for adults and children over 12 years of age (21 CFR 341). The individual components of the product are discussed below.

Ibuprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID). Like other NSAIDs, it has analgesic, antipyretic, and anti-inflammatory properties. Ibuprofen was first approved for prescription use in 1969 and for OTC use in the UK and US in 1983 and 1984, respectively. Since then, it has become widely used for the temporary relief of acute pain and fever. The Sponsor notes that in the US alone, approximately 13 billion adult doses (200 mg) of Ibuprofen were sold in 2004. Wyeth Consumer Healthcare (WCH) markets Advil, a brand of Ibuprofen in the US. The chemical structure is shown below:



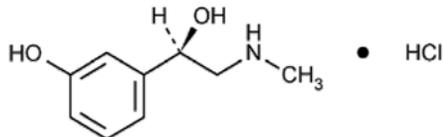
Molecular Formula: C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>

Molecular Weight: 206.28

Phenylephrine is a sympathomimetic amine that has been available for use as an OTC nasal decongestant since the early 1960s. PE acts predominantly by a direct effect on alpha-adrenergic receptors. In therapeutic doses, the drug has no substantial stimulant effect on the beta1-adrenergic receptors of the heart and does not stimulate beta2-adrenergic receptors of the bronchi or peripheral blood vessels. It is included as a Category I (safe and effective) oral nasal decongestant in the Final Monograph of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (21 CFR 341.20). The chemical structure is shown below:

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

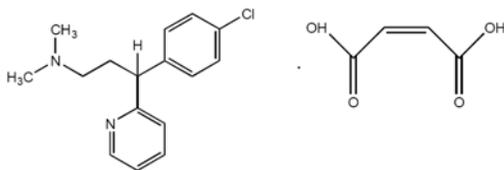
---



Molecular Formula:  $C_9H_{13}NO_2 \cdot HCl$

Molecular Weight: 203.67

Chlorpheniramine, a classical H<sub>1</sub>-receptor antagonist (antihistamine), has been available for more than 40 years as a nonprescription medication for relief of allergic rhinitis symptoms, and is included as a Category I (safe and effective) antihistamine in the Final Monograph of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (21 CFR 341.12). It has been shown to be effective against major histamine-mediated symptoms, *i.e.*, sneezing, itching and rhinorrhea. The safety and efficacy of chlorpheniramine has been demonstrated in clinical trials and through extensive therapeutic use. The chemical structure is shown below:



Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Molecular Weight: 390.86

## 2.2 Currently Available Treatment for Indications

Single ingredient pain relievers containing ibuprofen, single ingredient antihistamines containing chlorpheniramine, and single ingredient decongestants containing phenylephrine are readily available and could be combined to treat the indications or relieve the symptoms covered by the Advil Allergy Sinus product. Other combination products with the same ingredients as Advil Allergy Sinus are not available at the time of this review. However, combinations containing a pain reliever and an antihistamine, a pain reliever and a decongestant, and an antihistamine and a decongestant are available.

## 2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients ibuprofen, chlorpheniramine, and phenylephrine are readily available in the United States.

## 2.4 Important Issues With Pharmacologically Related Products

A Citizen's Petition has questioned the efficacy of oral phenylephrine as a decongestant. This issue was addressed in a Nonprescription Drug Advisory Committee (NDAC) meeting in December 2007. The NDAC determined that phenylephrine 10 mg has some effectiveness and should remain on the market. The NDAC also voted to encourage industry to study higher doses of phenylephrine.

## 2.5 Presubmission Regulatory Activity

The caplet formulation of the combination of ibuprofen, pseudoephedrine, and chlorpheniramine was approved for OTC marketing on December 12, 2002 (NDA 21-441). The product was indicated for use in the temporary relief of symptoms associated with hay fever or other respiratory allergies, and the common cold. The product is being reformulated with phenylephrine in place of pseudoephedrine in response to the methamphetamine act.

The following outlines FDA-WCH interactions on this program:

- March 23, 2005: WCH submitted a meeting request to discuss the clinical development plan for the ibuprofen + phenylephrine + chlorpheniramine combination product.
- May 10, 2005: a pre-IND teleconference was conducted concerning the clinical development plan.
- October 19, 2005: FDA told the Sponsor that the ibuprofen + phenylephrine + chlorpheniramine bioavailability study met all the requirements for exemption from the IND regulations.
- In the Pre-NDA Meeting Briefing Document dated February 23, 2007 Wyeth agreed to provide FDA with updated stability data for the (b) (4) Caplet formulations during NDA review.
- March 19, 2007: Pre-NDA meeting. Based on FDA input, the clinical development plan for the Ibuprofen 200 mg + Phenylephrine 10 mg + Chlorpheniramine 4 mg caplet consisted of one biopharmaceutic study (AD-05-05) comparing the combination caplet Ibuprofen 200 mg + Phenylephrine 10 mg + Chlorpheniramine 4 mg (fasted and fed) to a Motrin IB tablet (ibuprofen 200 mg/tablet), Sudafed PE tablet (phenylephrine 10 mg/tablet), and a Chlorpheniramine-Trimeton Allergy tablet (chlorpheniramine 4 mg/tablet) single ingredient products administered concomitantly in the fasted state.
- On September 25, 2007 WCH submitted the NDA for (b) (4) caplet

## 2.6 Other Relevant Background Information

In a filing-related communication in December 2007, FDA requested that the Sponsor submit the following chemistry, manufacturing and controls information:

- Provide updated drug product stability data for the to-be-marketed formulation
- Provide method validation protocols for Methods A7277 and A7300.

- The protocols should include experimental details for the forced degradation study and the method used to assess peak purity.

For Wyeth's response on December 18, 2007 see section 3.1 below.

On January 16, 2008 the Agency requested that Wyeth perform a 14-day general toxicity study to qualify the amount of the degradant, (b) (4), in the formulation, or provide justification as to why a study is not needed. In one of the qualification studies the stability profile for the degradants fell below the target levels for specification during testing. Wyeth's complete response is pending; however, they have indicated that a (b) (4) in the combination product produces less degradant over time and thus the qualification study is adequate.

### **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

#### **3.1 CMC (and Product Microbiology, if Applicable)**

The chemistry reviewer will address the CMC portion of this submission. One issue to be addressed is whether the sponsor's dissolution study is adequate to bridge the proposed formulation with the formulation used in the bioequivalence study. In addition, during the evaluation 6-month accelerated stability data for the optimized formulation, the Sponsor reported that (b) (4), a previously unreported degradant of phenylephrine and maleic acid had been detected. In an amendment submitted on December 18, 2007, the Sponsor is proposing to establish a specification for this degradant in the 12-month stability report based on data generated through 12 months. The Sponsor also noted that the planned inspection for the product manufacturing facility will be ready for inspection in April 2008 rather than January 2008. The chemistry reviewer will also evaluate these additional data.

#### **3.2 Animal Pharmacology/Toxicology**

The (b) (4) formulation utilizes a wet granulation process. During development of the caplet several degradation products were noted. All of these degradants fall below the International Conference on Harmonization (ICH) qualification limit of 0.5% of the pharmaceutically active material, and thus are in an acceptable range, except for the degradant, (b) (4). The Sponsor has conducted a qualification program for (b) (4) and has submitted the data. The FDA pharmacology-toxicology reviewer will review whether the pre-clinical toxicology studies performed with the product and its degradants are adequate

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

In support of the current submission, the Sponsor provided results of one bioequivalence trial (AD-05-05), a safety update including a literature search, and the proposed OTC labeling. All of these data are being evaluated in this review.

### **4.2 Tables of Clinical Studies**

There is only one clinical study submitted with this NDA application, study AD-05-05, which is described in sections 6 and 7 and in their subsections.

### **4.3 Review Strategy**

This review focuses on the safety update. The efficacy data for the clinical bioequivalence study #AD-05-05 is shown in section 6: however, the biopharmaceutics reviewer from the Office of Clinical Pharmacology and Biopharmaceutics will evaluate these data. The chemistry reviewer from the Division of Chemistry will evaluate the dissolution data bridging the current formulation with the formulation used in study #AD-05-05. The chemistry and pharmacology-toxicology reviewers will evaluate the additional information regarding the (b) (4) degradant the Sponsor submitted on December 18, 2007 and the data on the (b) (4) degradant the Sponsor was asked to provide on January 16, 2008.

### **4.4 Data Quality and Integrity**

The Principal Investigator of this study was Aziz Laurent, MD. The study was conducted at (b) (4). The Clinical, Statistical, and Pharmacokinetic Reports were prepared jointly by the Clinical and Biostatistical Departments of WCH. The clinical portion of the report was prepared by (b) (4), Research Fellow. The statistical portion of the report was prepared by and the statistical analysis was conducted by (b) (4) PhD, Principal Biostatistician. Wyeth Consumer Healthcare certifies that it did not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetics Act in connection with this application for (b) (4) NDA 22-113.

A DSI audit for the study site or data analysis is scheduled to be performed in April 2008.

### **4.5 Compliance with Good Clinical Practices**

Not applicable to this review.

## 4.6 Financial Disclosures

The Sponsor conducted one new clinical study (#AD-05-05) that involved only one clinical site and only one investigator. The Sponsor has submitted Form 3454 certifying no financial interest by the investigator.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

The bioequivalence data from study AD-05-05 submitted with this application will be analyzed by the biopharmaceutics reviewer. The study design, methods and results are shown below.

#### Study Design:

Study AD-05-05 was a single-dose, randomized, open-label, three-way crossover food effect/formulation effect study that examined the effects of food and formulation. Forty-one subjects were enrolled (19 males and 22 females) with forty subjects completing all three treatment periods (more than the 36 subjects that the Sponsor had calculated were required to complete the study in order to provide at least 80% power of declaring bioequivalence). The objectives evaluated were:

- The characterization of the rate and extent of absorption of ibuprofen, phenylephrine, and chlorpheniramine from (b) (4) caplet when administered under fasted and fed conditions.
- The characterization of the rate and extent of absorption of ibuprofen, phenylephrine, and chlorpheniramine from (b) (4) caplet compared to ibuprofen 200 mg, phenylephrine 10 mg, and chlorpheniramine 4 mg single entity products administered concomitantly in the fasted state.

The healthy volunteer male and female subjects received a single dose of one of the following treatments during each of the three treatment periods:

- **Treatment A:** one caplet containing ibuprofen 200 mg, phenylephrine 10 mg, and chlorpheniramine 4 mg under fasted conditions.
- **Treatment B:** one caplet containing ibuprofen 200 mg, phenylephrine 10 mg, and chlorpheniramine 4 mg under fed conditions.
- **Treatment C:** one Motrin IB tablet (ibuprofen 200 mg/tablet), one Sudafed PE tablet (phenylephrine 10 mg/tablet), and one Chlorpheniramine-Trimeton Allergy tablet (chlorpheniramine 4 mg/tablet) administered concomitantly under fasted conditions.

Study Endpoints:

The endpoints of study AD-05-05 included a comparison of AUC, C<sub>max</sub>, T<sub>max</sub> (and other biopharm parameters) between the ingredients of the proposed combination product and current marketed single ingredient products for ibuprofen, phenylephrine, and chlorpheniramine.

Study Methods:

An authorized Institutional Review Board approved the protocol, consent form, and all subject recruitment materials for study AD-05-05. After providing informed consent, potential subjects underwent a baseline screening, which consisted of a medical history, physical examination including vital signs, and fasting laboratory studies. Females had a urine-based pregnancy test at screening and prior to each treatment period. Prior to the start of the study, there was a review of all inclusion/exclusion criteria to re-affirm the subjects' eligibility for entry into the study. Subjects received one of the three treatments on three separate occasions according to a computer-generated randomization schedule. Treatment Periods I and II were separated by 14 days because of a holiday weekend.

Treatment Periods II and III were separated by 7 days. For each treatment period, 19 blood samples (7 mL each) were collected in heparin tubes over 72 hours (133 mL/treatment period and 399 mL for three treatment periods excluding blood required for screening evaluations). Samples through 16 hours after dosing were analyzed for all three drugs. During each treatment period, subjects were housed in the clinic from the evening before dosing until approximately 36 hours post-dose. Subjects returned on an outpatient basis for the 48- and 72-hour blood draws. At the conclusion of the study, the physical examination was repeated and the subject was discharged from the study. A physical examination was also done at any time a subject prematurely discontinued from the study. All adverse events (AE) that occurred during the study as well as any that were voluntarily reported by subjects within 15 days of completing the study were recorded.

Efficacy Findings:

The efficacy findings from study AD-05-05 are outlined below. Table 1 and Figure 1 below show ibuprofen pharmacokinetic (PK) parameters and mean plasma concentrations.

*Comment:*

*While it appears that the Sponsor's proposed combination product meets the criteria for bioequivalence, the biopharmaceutics reviewer will analyze these data and determine if they are adequate to support approval. One potential issue is whether the delay in the T<sub>max</sub> for phenylephrine in the presence of food is clinically significant or not.*

**Table 1. Study AD-05-05, ibuprofen pharmacokinetic parameters (n=40; mean, standard deviation, and 90% confidence intervals are shown).**

{NDA 22-113}

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

Treatment	AUCL (mcg.h/mL)	AUCI (mcg.h/mL)#	C <sub>max</sub> (mcg/mL)	T <sub>max</sub> (Hour)	t <sub>1/2</sub> (Hour)#
Mean (S.D.)					
A	73.01 (14.16)	74.19 (14.16)	20.40 (4.29)	2.17 (1.05)	2.15 (0.47)
B	65.70 (14.58)	67.26 (14.65)	19.27 (6.76)	1.91 (1.41)	2.22 (0.39)
C	73.31 (18.37)	74.60 (18.22)	22.08 (5.93)	1.80 (0.94)	2.15 (0.59)
Ratio (90% CI) ^					
B/A* %	89.64	89.61	90.21	--	--
	(85.14-94.38)	(85.24-94.21)	(81.72-99.58)	--	--
A/C* %	101.19	100.86	94.79	--	--
	(96.11-106.54)	(95.99-105.98)	(85.86-104.65)	--	--

BEST AVAILABLE  
COPY

Treatment: A: Caplet – Fasted; Treatment B: Caplet – Fed; Treatment C: Single ingredients administered concomitantly – Fasted.

^: Based on fitted log transformed parameters. \*: Reference product. #: Subject No. 108's concentration for treatment B did not exhibit a log linear elimination phase and thus AUCI and t<sub>1/2</sub> could not be computed. Consequently, the ratio and 90% CI for Ln AUCI, as well as the summary statistics for AUCI and t<sub>1/2</sub> for treatment B were based on 39 subjects.

Figure 1. Study AD-05-05, mean ibuprofen plasma concentration over time.

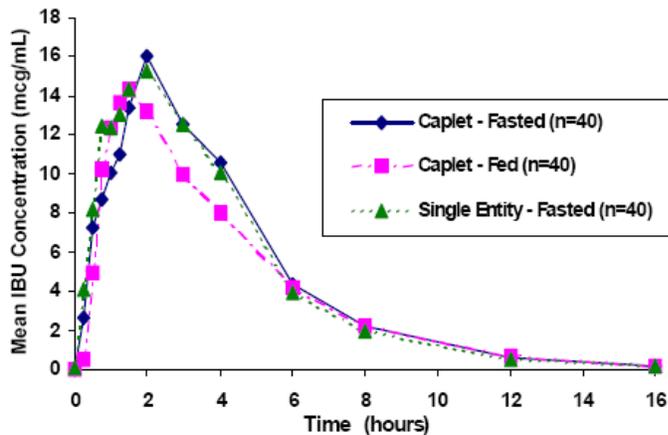


Table 2 and Figure 2 below show phenylephrine PK parameters and mean plasma concentrations.

Table 2. Study AD-05-05, phenylephrine pharmacokinetic parameters (n=40; mean, standard deviation, and 90% confidence intervals are shown).

Treatment	AUCL (ng.h/mL)	AUCI (ng.h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (Hour)	t <sub>1/2</sub> (Hour)
Mean (S.D.)					
A	222.69 (67.60)	227.57 (67.34)	67.61 (25.21)	1.10 (0.46)	2.02 (0.42)
B	204.02 (68.77)	209.06 (68.26)	60.67 (19.91)	1.73 (0.82)	1.96 (0.32)
C	221.29 (67.15)	226.63 (66.98)	70.39 (23.87)	1.06 (0.46)	1.98 (0.34)
Ratio and 90% CI^					
B/A* %	90.71	91.09	90.55	--	--
	(87.27-94.30)	(87.79-94.52)	(84.70-96.79)	--	--
A/C* %	100.66	100.46	95.01	--	--
	(96.84-104.64)	(96.81-104.25)	(88.87-101.57)	--	--

Treatment: A: Caplet – Fasted; Treatment B: Caplet – Fed; Treatment C: Single ingredients administered concomitantly – Fasted.

^: Based on fitted log transformed parameters. \*: Reference product. +: From the weighted (by sample size) average of PK values of AUCI, C<sub>max</sub> and T<sub>max</sub> from eight studies based on males only.

**Figure 2. Study AD-05-05, mean phenylephrine plasma concentration over time.**

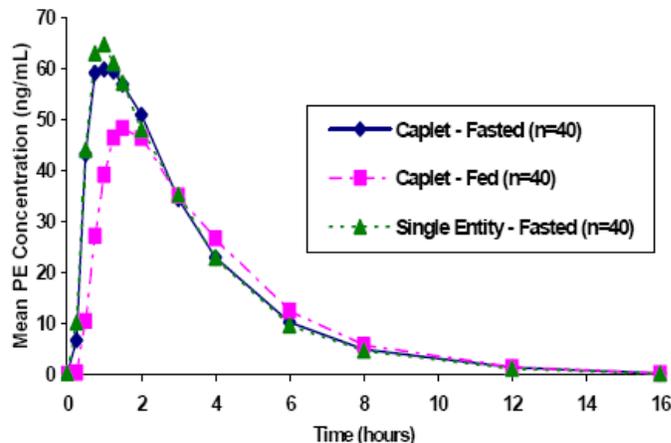


Table 3 and Figure 3 below show chlorpheniramine PK parameters and mean plasma concentrations.

**Table 3. Study AD-05-05, chlorpheniramine pharmacokinetic parameters (n=40; mean, standard deviation, and 90% confidence intervals are shown).**

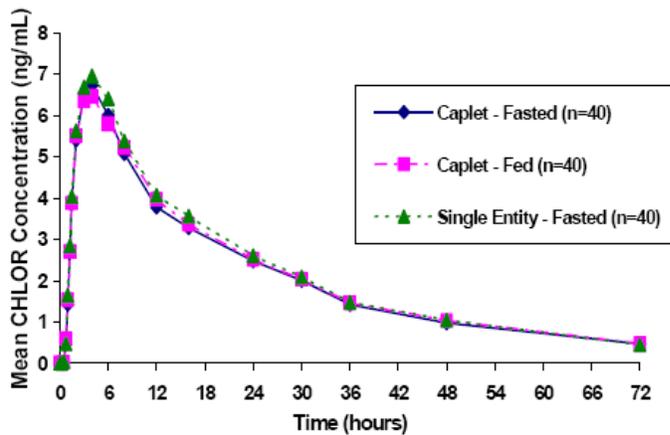
Treatment	AUCL (ng.h/mL)	AUCI (ng.h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (Hour)	t <sub>1/2</sub> (Hour)
Mean (S.D.)					
A	149.54 (51.73)	169.50 (68.97)	7.11 (1.61)	4.03 (1.25)	19.35 (8.40)
B	151.72 (52.86)	171.80 (66.28)	7.21 (1.55)	3.73 (1.57)	19.81 (7.28)
C	158.03 (51.60)	175.33 (62.47)	7.47 (1.66)	3.86 (1.38)	18.79 (5.70)
Ratio and 90% CI <sup>^</sup>					
B/A* %	101.40 (98.07-104.83)	101.93 (98.27-105.72)	101.80 (98.46-105.26)	--	--
A/C* %	93.81 (90.73-96.99)	94.98 (91.57-98.52)	95.18 (92.05-98.41)	--	--

Treatment: A: Caplet – Fasted; Treatment B: Caplet – Fed; Treatment C: Single ingredients administered concomitantly – Fasted.

<sup>^</sup>: Based on fitted log transformed parameters.

\*: Reference product.

**Figure 3. Study AD-05-05, mean chlorpheniramine plasma concentration over time**



### Efficacy Conclusions:

Under fasting conditions, the rate (C<sub>max</sub>) and extent (AUC) of absorption of the single entity marketed products containing ibuprofen (Motrin IB), phenylephrine (Sudafed PE), and chlorpheniramine (Chlor-Trimeton Allergy) appear to be equivalent to the combination caplet. However, in the presence of food, the T<sub>max</sub> for phenylephrine was delayed.

### *Comment:*

*As noted in section 6.1.14, the biopharmaceutics reviewer will evaluate the adequacy of Study AD-05-05 in establishing bioequivalence of the combination product with the individual ingredients.*

## **5.2 Pharmacodynamics**

No new pharmacodynamics data were submitted with this application.

## **5.3 Exposure-Response Relationships**

No new exposure-response data were submitted with this application.

# **6 INTEGRATED REVIEW OF EFFICACY**

## **6.1 Indication**

For the temporary relief of the following symptoms associated with hay fever or other respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor aches and pains, and fever. The product is intended for use for up to (b) (4) consecutive days for pain, up to 7 consecutive days for the treatment of nasal congestion, and up to 3 consecutive days for the treatment of fever.

### **6.1.1 Methods**

See section 5.1.

### **6.1.2 General Discussion of Endpoints**

See section 5.1.

### **6.1.3 Study Design**

See section 5.1.

### **6.1.4 Efficacy Findings**

See section 5.1.

### **6.1.5 Clinical Microbiology**

Not applicable to this submission.

### **6.1.6 Efficacy Conclusions**

See section 5.1.

## **7 INTEGRATED REVIEW OF SAFETY**

### **7.1 Methods and Findings**

The overall evaluation of safety for the (b) (4) caplet containing ibuprofen 200 mg/ phenylephrine 10 mg/ chlorpheniramine 4 mg, included adverse event data from one clinical study (bioequivalence study AD-05-05), a review of the Sponsor's adverse event database, data from the FDA AERS database, and a review of the literature.

The bioequivalence study AD-05-05 was designed as a three way crossover bioavailability/food effect study, and was described earlier in section 5.1 of this review. Details of the safety data from this study are described below in this section its subsections. The safety population consisted of all subjects who took study medication. Overall, there were no serious AEs reported during the study, and there were no significant safety findings related to the study product.

With regard to the individual ingredients in the combination product, ibuprofen has an extensive history of use. As an OTC analgesic/fever reducer, ibuprofen has been available for use in adults since 1984 (NDA 18-989). Phenylephrine is a monograph ingredient in the 1976 Final Monograph of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use. As an OTC nasal decongestant, phenylephrine is indicated for use in adults and in

children 2 years of age and older. Chlorpheniramine is a first generation antihistamine, patented in 1958, and is a monograph ingredient in the Final Monograph of Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use.

In support of the safety and efficacy of the proposed combination product, the Sponsor referred to the following NDAs for support of the safety and efficacy of ibuprofen and the combination of ibuprofen with an oral nasal decongestant: NDA 18-989 (Advil Tablets/Caplets/Gel caplets), NDA 19-771 (Advil Cold & Sinus Tablets/Caplets), and NDA 20-402 (Advil Liqui-Gels). The Sponsor states that these referenced NDAs included clinical studies supporting the efficacy and safety of ibuprofen in tablet/caplet/gel caplet/liquigel form as an analgesic/antipyretic for use in adults and children 12 years of age or older and clinical studies supporting the efficacy and safety of an ibuprofen/pseudoephedrine combination for the temporary relief of symptoms of nasal congestion, headache, fever, and body aches. The Sponsor also referred to NDA 21-441 (Advil Allergy Sinus caplets) in support of the efficacy and safety of an ibuprofen/pseudoephedrine/chlorpheniramine combination caplet in the treatment of allergic rhinosinusitis.

*Comments:*

*1. In the reports of studies submitted to support approval for two of the referenced NDAs above, (b) (4) and 19-771, this reviewer could not find how many pediatric patients were included.*

*2. For NDA 20-402, Advil Migraine Liqui-Gels with an indication of migraine headache relief, the Sponsor included some (actual number is not clear) patients ages 12-17; however, the neurology medical officer reviewers, Drs. Oliva and Levin, concluded that “there were too few adolescent patients to provide sufficient evidence to support the treatment of migraines in adolescents” and that the Sponsor should perform additional studies in adolescents.*

*3. For NDA 21-441, Advil Allergy Sinus Caplets, the Sponsor included 150 patients in the age range 12 and older in the pivotal study (AD-99-02) of 1070 patients. Of note, adverse events in this group were fewer on a percentage basis than in three older age groups.*

*4. In summary, some pediatric patients ages 12-17 were included in at least 2 of the referenced NDAs, but apparently no subjects younger than age 12 were included.*

The Sponsor’s literature search was performed on the combination of ibuprofen, phenylephrine, and chlorpheniramine utilizing the following databases: Medline, Biosis Previews, Toxfile, EMBASE, SciSearch, and the Derwent Drug File, from 1950 to June 11, 2007. This search did not yield any references concerning the safety of the drug combination.

*Comment:*

*The combination product literature search did not yield any references because it has not been marketed in the USA, and apparently not in other countries. This reviewer is not familiar with the databases other than Medline and Toxfile.*

The Sponsor also performed a separate search for safety-related ibuprofen literature. Per agreement with FDA, the Sponsor cross-referenced to the literature review it submitted with sNDA 18-989 (submitted to FDA on January 31, 2006). The literature contained in the current application is an update to that review and covers the period October 2005 to June 11, 2007. The current search yielded 54 papers distributed among various organ systems, syndromes or subjects, including cardiovascular effects. These papers are summarized in Table 8 in section 8.6. The literature review did not reveal any unique adverse events that have not been reported previously.

The proposed product's safety profile was examined using a five-year interval of spontaneous adverse event (spontaneous AE) reports. Two sources of spontaneous AEs were used: AERS data and Sponsor data. These data are reviewed in section 7.1.17 of this review.

### **7.1.1 Deaths**

There were no deaths reported during Study AD-05-05.

### **7.1.2 Other Serious Adverse Events**

There were no serious AEs reported during Study AD-05-05. Serious AEs from the Sponsor's database and the AERS search are reviewed in section 7.1.17 of this review.

### **7.1.3 Dropouts and Other Significant Adverse Events**

In Study AD-05-05, one subject (No. 212) voluntarily withdrew from the study during the first treatment period due to difficulty in blood draws.

#### **7.1.3.1 Overall profile of dropouts**

In Study AD-05-05, one subject (No. 212) voluntarily withdrew from the study during the first treatment period due to difficulty in blood draws.

#### **7.1.3.2 Adverse events associated with dropouts**

In Study AD-05-05, one subject (No. 212) voluntarily withdrew from the study during the first treatment period due to difficulty in blood draws.

#### **7.1.3.3 Other significant adverse events**

There were no other significant adverse events reported during Study AD-05-05.

## 7.1.4 Other Search Strategies

## 7.1.5 Common Adverse Events

### Adverse events characteristic of pharmacologic class:

#### **Ibuprofen**

Due to widespread use of ibuprofen its AE profile is well characterized. The most frequently reported AEs associated with NSAID use involve the gastrointestinal (GI) tract, such as dyspepsia, and abdominal pain. Serious AEs such as peptic ulcer and GI bleeding can occur. Central nervous system effects, such as headache, dizziness, or nervousness are also reported. Occasionally, renal insufficiency (or renal failure) and dermatologic (rash) adverse events are reported. The incidence and severity of AEs are usually dose and duration of use dependent. With use at low doses and for short periods of time, as with OTC use over about 10 days, the frequency and severity of AEs are less frequent and less severe than seen with prescription use.

Recently, questions have been raised about the cardiovascular risks associated with both all non-aspirin NSAIDs and not simply with the COX-2 inhibitors. While there is no data to suggest that short term, low-dose use of non-aspirin NSAIDs is associated with an increased risk of cardiovascular events, with long term use there may be an increased risk with all non-aspirin NSAIDs, which appears to be dose and duration of use dependent. In addition, when using low dose aspirin for cardioprotection, and depending on the timing of the dosing of ibuprofen, there can be an interference with aspirin's antiplatelet effect. The cardiovascular risk data for ibuprofen is discussed in section 8.6 of this review.

#### **Phenylephrine**

Sympathomimetic drugs like phenylephrine can be associated with AEs such as anxiety, nervousness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse. In low-therapeutic doses, PE causes little central nervous system stimulation, though a few patients may be sensitive to this effect. As with other sympathomimetic drugs, PE should be used with caution in hypertensive subjects, diabetes mellitus, ischemic heart disease, or prostatic hypertrophy.

#### **Chlorpheniramine**

Chlorpheniramine is a first-generation antihistamine. The most common AEs associated with first-generation antihistamines are associated with central nervous system depression, including drowsiness, somnolence, asthenia, dizziness, and incoordination. First-generation antihistamines may also stimulate the CNS, a paradoxical response that is more commonly seen in children. Other AEs include headache, psychomotor impairment, and antimuscarinic effects such as dry mouth, urinary difficulty/retention, and constipation. Gastrointestinal effects are seen less often, but could include nausea, vomiting, diarrhea, and epigastric pain. Palpitations and arrhythmias have been reported occasionally with most antihistamines.

### Adverse events in study AD-05-05:

The safety population consisted of all subjects who took study medication. Forty-one subjects who received at least one dose of study medication were included in the safety population. One subject (No. 212) withdrew voluntarily during Period I and only received one treatment (caplet under fed conditions), whereas the other 40 subjects who completed the study were exposed to all three treatments. To account for this, the denominator for each treatment's AE incidence rate was based on the number of subjects exposed to the respective treatment.

The common, non-serious AEs reported in AD-05-05 are consistent with the known profile for ibuprofen, phenylephrine, and chlorpheniramine. All AEs that occurred during the study are summarized by MedDRA system organ classification, and further subcategorized by MedDRA preferred term in Table 4 below.

Throughout the study, 15 subjects reported 21 AEs. Two subjects (Nos. 206, 210) reported AEs in two periods and one subject (No. 220) reported AEs in three periods. Seven AEs were reported by seven subjects (17.5%) following the caplet fasted treatment, five AEs were reported by five subjects (12.2%) following the caplet fed treatment, and nine AEs were reported by seven subjects (17.5%) following the single entity treatment.

The most common AE among all treatments was headache (four incidences across treatments), followed by dizziness and dyspepsia (three incidences across treatments for each). All but two AEs were rated as mild; the other two were rated as moderate. The investigator assessed that all but two AEs were unrelated to the study medications. No notable differences among the treatments were seen in the individual AE rates.

**Table 4. Number of adverse events by MedDRA preferred term in study AD-05-05.**

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

Body System/ Symptom	Treatment Group*		
	A	B	C
Gastrointestinal			
Dyspepsia	1	1	1
Nausea	1	0	1
Vomiting	1	0	0
General Disorders, Administration Site			
Fatigue	0	1	0
Nervous System			
Dizziness	1	1	2
Headache	1	2	0
Reproductive System/Breast Disorders			
Metrorrhagia	1	0	0
Respiratory, Thoracic, Mediastinal			
Cough	0	0	1
Dry Throat	1	0	0
Nasal congestion	0	0	1
Pharyngolaryngeal Pain	0	0	1
Rhinorrhea	0	0	1
Skin and Subcutaneous Disorders			
Swelling Face	0	0	1

\* Treatment A = IBU 200 mg + PHE 10 mg + CHLOR 4 mg caplet fasted  
 Treatment B = IBU 200 mg + PHE 10 mg + CHLOR 4 mg caplet fed  
 Treatment C = Motrin IB 200 mg tablet + Sudafed PE 10 mg caplet + Chlor-Trimeton 4 mg tablet fasted

**Comment:**

*IBU, PHE, and CHLOR refer to ibuprofen, phenylephrine, and chlorpheniramine, respectively in Table 4 above. Headache and dizziness were the most common AEs. While 15 of 41 subjects reported a total of 21 AEs, the incidence of individual AEs is low overall, there was no placebo comparator, and there were no serious AEs. We cannot make any firm conclusion about the likelihood of seriousness of AEs in a larger population from this study.*

**7.1.5.1 Eliciting adverse events data in the development program**

Subjects in the bioequivalence trial (AD-05-05) were observed by the study personnel during the duration of the study. The reporting period for AEs started when the subject took the first dose of study medication. Serious AEs were reported any time they occurred after the subject signed the informed consent.

At the conclusion of the study, the physical examination was repeated and the subject was discharged from the study. A physical examination was also done at any time a subject

prematurely discontinued from the study. All adverse events (AE) that occurred during the study as well as any that were voluntarily reported by subjects within 15 days of completing the study were recorded.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse events observed during study AD-05-05 and adverse events in the Sponsor's database were grouped by preferred terms using MedDRA organ class terminology.

#### 7.1.5.3 Incidence of common adverse events

Adverse events that occurred during the bioequivalence trial (AD-05-05) are consistent with the known adverse event profile for ibuprofen, phenylephrine, or chlorpheniramine. No single AE occurred at a rate more than 2% in either treatment group.

#### 7.1.5.4 Common adverse event tables

The AEs seen in study AD-05-05 are shown in table X in section 7.1.5 above.

#### 7.1.5.5 Identifying common and drug-related adverse events

X adverse events reported during study AD-05-05 were rated as probably or definitely related to treatment.

#### 7.1.5.6 Additional analyses and explorations

There were no additional analyses or explorations performed by the Sponsor. Additional aspects of the safety update are presented in sections 7.3 and 7.4 of this review.

### 7.1.6 Less Common Adverse Events

The population and number of adverse events in study AD-05-05 were too small to assess the incidence of less common adverse events.

### 7.1.7 Laboratory Findings

All laboratory tests conducted for this submission were done in the bioequivalence study AD-05-05.

#### 7.1.7.1 Overview of laboratory testing in the development program

Pre-study, all subjects had a laboratory evaluation including a CBC, complete urinalysis, and serum chemistry profile. The serum chemistry profile consisted of albumin, alkaline phosphatase, bilirubin, BUN, calcium, CO<sub>2</sub>/HCO<sub>3</sub>, chloride, cholesterol, creatinine, gamma GT, globulin, glucose, lactate dehydrogenase, phosphate, potassium, protein, SGOT, SGPT, sodium,

triglycerides, uric acid. A pre-study drug screen and an HIV test were performed. Females had a pregnancy test at screening and prior to each treatment period.

At least one laboratory test was abnormal in 24 (58.5%) subjects during the screening evaluation, but none were clinically significant. No post-study laboratory tests were performed.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable.

#### 7.1.7.4 Additional analyses and explorations

Not applicable.

#### 7.1.7.5 Special assessments

Not applicable.

### 7.1.8 Vital Signs

The only study with (b) (4) that monitored vital signs was the bioequivalence study AD-05-05 in 41 subjects. Blood pressure, heart rate, respirations, and oral temperature were measured at baseline and at the end of the study. There were no clinically significant changes in vital signs during the study.

### 7.1.9 Electrocardiograms (ECGs)

The only study of (b) (4) that monitored electrocardiograms was the bioequivalence study AD-05-05 in 41 subjects. The ECG of each subject was recorded at baseline and at the end of the study. There were no clinically significant changes in ECGs during the study.

### 7.1.10 Immunogenicity

There are no known immunogenicity issues related to ibuprofen, phenylephrine, or chlorpheniramine.

### 7.1.11 Human Carcinogenicity

There are no known carcinogenicity issues related to ibuprofen, phenylephrine, or chlorpheniramine.

### **7.1.12 Special Safety Studies**

There was no special safety studies requested by FDA or performed by the Sponsor for this application.

#### **7.1.13 Withdrawal Phenomena and/or Abuse Potential**

There are no reports of withdrawal phenomena for any of the individual ingredients, ibuprofen, phenylephrine, or chlorpheniramine of the (b) (4) product.

*Comment:*

*Since the combination product has not been marketed before, an inquiry to the Drug Abuse Warning Network (DAWN) would not yield data on the abuse potential with use of the product. As a single ingredient, ibuprofen misuse has been reported in self-poisoning attempts. However, there is no withdrawal phenomenon or addiction potential reported for ibuprofen, phenylephrine, or chlorpheniramine.*

### **7.1.14 Human Reproduction and Pregnancy Data**

There was no new reproduction or pregnancy data submitted to support this application. The proposed label contains an appropriate pregnancy warning for OTC drug products containing ibuprofen, phenylephrine, and chlorpheniramine. The proposed label warns pregnant and breast-feeding women to ask a health professional before use, and warns pregnant women to not use ibuprofen in the last 3 months of pregnancy unless directed by a doctor to do so, since it (ibuprofen) may cause problems in the unborn child or complications during delivery.

### **7.1.15 Assessment of Effect on Growth**

There were no new data submitted with this application on the effect on growth. Ibuprofen is approved for use in children down to 6 months of age. Phenylephrine and chlorpheniramine have been used in children as single ingredients or in combinations as cough, cold products. There were no literature references in section 8.6 that discussed an effect on growth. Given that there is a knowledge base for each of the ingredients through extended use over more than two decades, it is not expected that there will be any effect on growth.

### **7.1.16 Overdose Experience**

To evaluate overdose experience, the Sponsor submitted data from the American Association of Poison Control Centers (AAPCC). Since an ibuprofen, phenylephrine, and chlorpheniramine is not currently marketed in the U.S., the case selection strategy consisted of extracting all cases for 19xx-20xx where a single ingredients were reported to have been co-ingested.

### 7.1.17 Postmarketing Experience

There is no postmarketing experience with the combination product as it has not been marketed in the USA or overseas. The Sponsor assessed postmarketing safety by collating and analyzing adverse event reports from its database and the FDA MedWatch database (AERS) in which concomitant use of the individual ingredients, ibuprofen, phenylephrine, and chlorpheniramine was mentioned. Data from the Sponsor database consisted of both electronic records and copies of all MedWatch report forms prepared by the company. The interval spanned by the Sponsor data was April 30, 2001 to August 15, 2006 and the interval spanned by the AERS data was April 1, 2001 to March 31, 2006.

A total of 51 spontaneous AE cases, documenting exposure to ibuprofen, phenylephrine and chlorpheniramine at any dose were extracted from the two databases: 8 Sponsor cases and 43 AERS cases. The extracted cases were assigned to one of four cohorts: Suspect, Interacting, Concomitant, or Mixed based on the reporter’s determination of the product role codes. These cases are shown below in Table 5.

**Table 5. Principal coding terms associated with each case cohort (SOC nomenclature)**

Cohort name	Total Unique MedDRA terms	System Organ Class	Total Unique MedDRA terms by SOC
<i>AERS Cases</i>			
All Cases n = 43	220*	Investigations	33
		Nervous System Disorders	21
		Infections and Infestations	19
		Hepatobiliary Disorders	17
		Musculoskeletal and Connective Tissue Disorders	15
Suspect n = 31	71	Nervous system Disorders	17
		Cardiac Disorders	10
		Psychiatric Disorders	8
		Investigations	7
		Gastrointestinal Disorders	6
Concomitant n = 10	167	Investigations	28
		Infections and Infestations	19
		Hepatobiliary Disorders	17
		Musculoskeletal and Connective Tissue Disorders	14
Mixed n = 2	8	Psychiatric Disorders	3
		Cardiac Disorders	1
		General Disorders and Administration Site Conditions	1
<i>Sponsor Cases</i>			
All Cases n = 8	15	General disorders and administration site disorders	5
		Infections and infestation	3
		Nervous system disorders	3
Suspect n = 1	5	Nervous system disorders	2
Mixed n = 7	10	General disorders and administration site disorders	5
		Infections and infestation	3

\* When a term was reported in all three cohorts, the term would be counted only one time in the All Cases cohort; hence the sum of terms for each cohort may not equal the sum of terms for the All Cases cohort.

An individual adverse event case was considered serious when one or more of the following outcomes were noted in the report:

- death

- life threatening; inpatient hospitalization or prolongation of an existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly.

The suspect cohort was the primary data source for safety profile modeling. Cases were assigned to this group when the reporter designated ibuprofen, phenylephrine and chlorpheniramine - containing products as suspect drugs. Of the 51 total extracted cases, 32 cases (63%) were assigned to the Suspect cohort: 1 Sponsor case and 31 AERS cases.

Sponsor's database: case detail of the one serious AE case:

The Sponsor notes that initial information was received on November 19, 2001 from an attorney regarding a 44-year old white female patient who reportedly experienced a stroke. The attorney alleged that the patient received therapy with "PPA containing products" then experienced a hemorrhagic stroke, seizures, an atrial arrhythmia, vasospasm, and a severe elevation of blood pressure that resulted in significant disability or incapacity.

The patient had a past history of polysubstance abuse and bipolar disorder. Her family history included "hypertension, aneurysm, arteriovenous malformation, circulatory disorder, cardiovascular disease, cardiac valvular disease, myocardial infarction, seizures disorders, bleeding disorders and migraines".

Over a two-week period in early December 2000 she had taken Tylenol Allergy Sinus (acetaminophen/ pseudoephedrine / chlorphenamine), Advil Cold and Sinus (ibuprofen / pseudoephedrine), Triaminic (chlorphenamine / phenylpropanolamine), Sudafed (pseudoephedrine), Benadryl Allergy / Sinus Headache (acetaminophen/ pseudoephedrine /diphenhydramine), Alka-Seltzer Plus Maximum Strength Sinus (aspirin / brompheniramine / phenylpropanolamine, and Dristan Cold Multi-symptom Formula (acetaminophen / chlorpheniramine / phenylephrine). Prescribed medication included included Synthroid (levothyroxine), Albuterol (salbutamol), Pamelor (nortriptyline), Fioricet (butalbital / caffeine / paracetamol), and Zomig (zolmitriptan).

The Sponsor's review of the medical records indicated the patient presented to the emergency department on (b) (6) after experiencing a headache, right-sided pain and tingling, left-sided weakness and tingling in her extremities and lips, sensitivity to noise and lights and vision blackness. The patient was hospitalized for a possible stroke. Cardiovascular exam revealed a pulse rate of 80 beats per minute with a regular rate and rhythm; blood pressure was 100/60 mm Hg. Magnetic resonance imaging (MRI) showed a possible stroke; magnetic resonance angiography (MRA) revealed a left anterior insular branch, middle cerebral artery occlusion, and an electro-encephalogram was negative. The patient's headache improved with Naprosyn and Toradol. The patient's strength on the life side returned to normal and her visual symptoms resolved almost completely upon discharge. On (b) (6) a neurological examination revealed no abnormalities. There was no facial, palatal, or lingual weakness. Carotid pulsations were felt bilaterally and no bruits were heard over the neck or head. Muscle strength appeared to be normal in upper and lower extremities. Sensory examination and cerebellar tests were within normal limits. On (b) (6) a neurologist reviewed the patient's December 2000 MRI and

{NDA 22-113}

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

MRA and saw no abnormalities. The physician suggested the patient's symptoms were "very likely psychogenic, related to her underlying bipolar disorder."

*Comment:*

*This one serious adverse event case from the Sponsor's database cannot clearly be attributed to an adverse event due to ibuprofen, phenylephrine, or chlorpheniramine.*

Of the 31 cases extracted from the AERS database, 23 listed a serious outcome; the single case found in the sponsor database was also listed among these 23 cases. All 23 cases appear to be confounded by the presence of phenylpropanolamine (PPA), which the reporter also noted as being an additional suspect drug. Based on dates FDA received these reports, they may have been reported due to publicity surrounding the withdrawal of PPA from the OTC market.

The Sponsor tabulated the major Preferred Terms and grouped them according to the MedDRA System Organ Class for each cohort. Table 6 below shows all the serious cases from the AERS database for which the concomitant use of ibuprofen, phenylephrine, and chlorpheniramine were suspected as the cause for the adverse event.

**Table 6. Tabulation of World-Wide Reported Events Extracted from the AERS Data Base and Encoded as MedDRA Terms for All Serious "Suspect" Cases for Ibuprofen - Phenylephrine – Chlorpheniramine.**

MedDRA System Organ Class	Preferred Term	Total	Domestic Report Source						ex-U.S. Report Source					
			Healthcare Professional		Non-healthcare Professional		Not Specified		Healthcare Professional		Non-healthcare Professional		Not Specified	
			Not Listed	Listed	Not Listed	Listed	Not Listed	Listed	Not Listed	Listed	Not Listed	Listed	Not Listed	Listed
<b>Blood and lymphatic system disorders</b>														
	Anemia	1	0	1	0	0	0	0	0	0	0	0	0	0
	<b>Subtotal</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Cardiac disorders</b>														
	Angina unstable	1	0	1	0	0	0	0	0	0	0	0	0	0
	Coronary artery disease	1	0	1	0	0	0	0	0	0	0	0	0	0
	Coronary artery occlusion	1	0	1	0	0	0	0	0	0	0	0	0	0
	Dilatation atrial	1	0	1	0	0	0	0	0	0	0	0	0	0
	Dilatation ventricular	1	0	1	0	0	0	0	0	0	0	0	0	0
	Myocardial infarction	2	2	0	0	0	0	0	0	0	0	0	0	0
	Sinus tachycardia	1	1	0	0	0	0	0	0	0	0	0	0	0
	Ventricular hypertrophy	1	0	1	0	0	0	0	0	0	0	0	0	0
	Ventricular hypokinesia	1	0	1	0	0	0	0	0	0	0	0	0	0
	<b>Subtotal</b>	<b>10</b>	<b>3</b>	<b>7</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Gastrointestinal disorders</b>														
	Dyspepsia	1	1	0	0	0	0	0	0	0	0	0	0	0
	Haematemesis	1	1	0	0	0	0	0	0	0	0	0	0	0
	Melaena	1	1	0	0	0	0	0	0	0	0	0	0	0
	Nausea	1	1	0	0	0	0	0	0	0	0	0	0	0
	Peptic ulcer	1	1	0	0	0	0	0	0	0	0	0	0	0

Clinical Review  
Steven Osborne, M.D.

{NDA 22-113}

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

Vomiting	1	1	0	0	0	0	0	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>6</b>	<b>6</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>General disorders and administration site conditions</b>														
Asthenia	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Chest pain	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Pain	22	0	1	0	0	0	21	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>24</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>22</b>	<b>0</b>						
<b>Injury, poisoning and procedural complications</b>														
Injury	23	0	2	0	0	0	21	0	0	0	0	0	0	0
Post procedural complication	1	0	1	0	0	0	0	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>24</b>	<b>0</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>21</b>	<b>0</b>						
<b>Investigations</b>														
Blood chloride decreased	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Blood glucose increased	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Blood sodium decreased	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Ejection fraction decreased	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Oxygen saturation decreased	1	0	1	0	0	0	0	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>5</b>	<b>0</b>	<b>5</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

MedDRA System Organ Class	Preferred Term	Total	Domestic Report Source						ex-U.S. Report Source						
			Healthcare Professional		Non-healthcare Professional		Not Specified		Healthcare Professional		Non-healthcare Professional		Not Specified		
			Not Listed	Listed	Not Listed	Listed	Not Listed	Listed	Not Listed	Listed	Not Listed	Listed	Not Listed	Listed	
	Osteoarthritis	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	Pain in extremity	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	<b>Subtotal</b>	<b>2</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>															
	Breast cancer	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	Malignant lymphoid neoplasm	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	<b>Subtotal</b>	<b>2</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Nervous system disorders</b>															
	Cerebellar infarction	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	Cerebral infarction	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	Cerebrovascular accident	1	1	0	0	0	0	0	0	0	0	0	0	0	0
	Convulsion	1	1	0	0	0	0	0	0	0	0	0	0	0	0
	Encephalomalacia	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	Encephalopathy	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	Headache	1	1	0	0	0	0	0	0	0	0	0	0	0	0
	Lacunar infarction	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	Mental impairment	5	0	0	0	0	0	5	0	0	0	0	0	0	0
	Mental retardation severity unspecified	1	0	0	0	0	0	1	0	0	0	0	0	0	0
	<b>Subtotal</b>	<b>14</b>	<b>3</b>	<b>5</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>6</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

Clinical Review  
Steven Osborne, M.D.

{NDA 22-113}

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

Psychiatric disorders														
Anxiety	21	0	0	0	0	0	0	21	0	0	0	0	0	0
Decreased activity	3	0	0	0	0	0	0	3	0	0	0	0	0	0
Mental disorder	1	0	0	0	0	0	0	1	0	0	0	0	0	0
<b>Subtotal</b>	<b>25</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>25</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Respiratory, thoracic and mediastinal disorders														
Dyspnoea	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Pneumonia aspiration	1	0	1	0	0	0	0	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>2</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Skin and subcutaneous tissue disorders														
Hyperhidrosis	1	1	0	0	0	0	0	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Surgical and medical procedures														
Triple vessel bypass graft	1	0	1	0	0	0	0	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Vascular disorders														
Deep vein thrombosis	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Haemorrhage	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Hypertension	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Hypotension	1	1	0	0	0	0	0	0	0	0	0	0	0	0
<b>Subtotal</b>	<b>4</b>	<b>3</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Grand Total</b>	<b>121</b>	<b>18</b>	<b>29</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>74</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

*Comment:*

*For the AERS database a total of 31 cases were listed as the Suspect case cohort. The Sponsor noted (and supported via a table in section 1.11.3.2 of the submission) that at least one phenylpropanolamine- (PPA-) containing product is also mentioned as a suspect product in each case. These data are shown in Table 7 below:*

**Table 7. Reporting Frequency of PPA-Containing Products found within the ibuprofen-phenylephrine-chlorpheniramine Suspect Dataset**

PPA Containing Product	Mention Frequency
Dimetapp	31
Tavist D	31
Alka Seltzer Plus Cold, Allergy	15
Alka-Seltzer Plus Cold	13
Phenylpropanolamine HCl	10
Contac 12 Hour	10
Entex LA	6
Alka-Seltzer Cold + Sinus	3
Alka-Seltzer Nighttime Cold	3
Coricidin D SRT	2
Dristan	2
BC Cold, Allergy Sinus Powder	2
Robitussin-CF	1
Triaminic	1

*Based on the dates that FDA received these cases, the Sponsor believes these reports were stimulated by the proposal to withdraw PPA-containing products from the U.S. OTC market, which occurred in November 2000. Since a PPA-containing product is also listed as a suspect drug for all cases in the Suspect case cohort, the reported events and outcomes are confounded with respect to the contribution of IBU, PHE and CHL to the reported events/outcomes. Hence, no inferences about the safety of the proposed combination can be drawn from the AERS Suspect case cohort. It is noteworthy that no fatalities were reported for the Suspect case cohort. Of note, in some instances more than one PPA-containing product was mentioned for an individual case. From these data no significant safety issues emerge for the proposed combination product.*

*The principal events, as MedDRA preferred coding terms, associated with these cases included: Injury (26 mentions), and Cerebrovascular accident (8 mentions).*

## **7.2 Adequacy of Patient Exposure and Safety Assessments**

### **7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**

The primary data for safety of the proposed combination product was obtained from Study AD-05-05 in which 41 subjects (40 completors) were treated with the proposed combination product in a 3-way crossover, single-dose bioequivalence trial. There are no other marketed products that combine the three ingredients (ibuprofen, phenylephrine, and chlorpheniramine) from which safety may be assessed. See section 7.2.2 below for secondary data sources for the safety evaluation.

#### **7.2.1.1 Study type and design/patient enumeration**

Study AD-05-05 treated 41 subjects with the proposed combination product in a 3-way crossover, single-dose bioequivalence trial.

#### **7.2.1.2 Demographics**

In Study AD-05-05 there were 19 males (46.3%) and 22 females (53.7%). The majority of the subjects were White (78.0%), followed by Black/African American (17.1%) and Asian (4.9%). With respect to ethnicity, 22.0% of the subjects were Hispanic/Latino. The average age, weight and height were 26.7 years (range: 18-42 years), 151.5 lbs (range: 106-207 lbs) and 67.5 inches (range: 61-78 inches), respectively. There was a significant treatment-by-gender effect for all three drugs: females had higher values for AUC and C<sub>max</sub>, and earlier T<sub>max</sub> values than for males. With respect to the extent of absorption for ibuprofen, phenylephrine, and chlorpheniramine, the within gender results were consistent with each other and with the overall population. While there were gender differences with rate of absorption of ibuprofen and chlorpheniramine, the differences were not clinically significant and are not expected to affect the safety or efficacy of the combination caplet.

### 7.2.1.3 Extent of exposure (dose/duration)

In Study AD-05-05, subjects each received a total dose of 600 mg ibuprofen, 30 mg phenylephrine, and 12 mg chlorpheniramine over a four-week period of three treatments. Subject 212 withdrew voluntarily during the first treatment period and only received ibuprofen 200 mg, phenylephrine 10 mg and chlorpheniramine 4 mg. For each treatment period, subjects received 200 mg ibuprofen, 10 mg phenylephrine, and 4 mg chlorpheniramine.

For a population exposure to the individual ingredients, the Sponsor tabulated domestic sales of OTC products containing ibuprofen, phenylephrine, and chlorpheniramine for the time period January 1, 2002 to June 18, 2006. Over the four and one-half year interval, approximately (b) (4) solid dose forms of single ingredient ibuprofen products were sold to consumers through retail food, drug and mass marketing chains; these data exclude sales through (b) (4) and discount club chains. Also during this time, approximately (b) (4) single ingredient and combination product solid dose forms containing chlorpheniramine and (b) (4) billion single ingredient and combination product solid dose forms containing phenylephrine were sold to consumers through mass marketing chains.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Data from the Sponsor's safety update is discussed in section 7.1.17 and data from the AERS Database is discussed in section 7.2.9. Safety data from the literature is discussed in section 8.2 of this review.

### 7.2.3 Adequacy of Overall Clinical Experience

This application requests substitution of a monograph decongestant, phenylephrine, for another decongestant, pseudoephedrine in a combination product with ibuprofen and chlorpheniramine. Each of the individual ingredients has been used for sufficient time and extent to understand their clinical effects. While this specific combination of ingredients has not been previously marketed as a combination product, there were no clinically significant drug-drug interactions in the Sponsor's database or in the literature review. The current safety data is adequate for OTC marketing.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal or in vitro data were not provided in this application.

### 7.2.5 Adequacy of Routine Clinical Testing

The bioequivalence study, #AD-05-05, performed for this submission is adequate.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Sponsor provided sufficient data to characterize the pharmacological profile of the combination product. There are no clinically significant metabolic or clearance issues identified

with the individual ingredients. Due to a potential hypertensive effect when phenylephrine is used with, or shortly after, a monoamine oxidase (MAO) inhibitor, the proposed label warns patients not to use the product with or for two weeks after taking a MAO inhibitor.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

#### 7.2.8 Assessment of Quality and Completeness of Data

#### 7.2.9 Additional Submissions, Including Safety Update

On January 25, 2008 the Sponsor submitted a 4-month safety update which included an additional literature search and adverse event reports from the Sponsor's database and from the AERS database.

The literature search covered the period from June 11, 2007 to December 11, 2007 and employed the same methods as the search noted in section 7.1.17 of this review. The search revealed 9 references describing adverse events distributed among different organs, but did not result in any safety reports involving the use of the proposed 3-drug combination.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

Common adverse events for the combination product are likely to be nonserious as all the ingredients are either an approved drug for OTC use (ibuprofen) or monograph drugs (phenylephrine and chlorpheniramine). Potentially serious adverse events could be gastrointestinal bleeding due to ibuprofen, hypertension or arrhythmias due to phenylephrine, or seizures due to chlorpheniramine. However, such serious adverse events from these ingredients are typically dose-related and are therefore not expected if the drug is used as labeled.

A limitation of the available safety data exists because the 3-drug combination product has not been previously marketed. While the Advil Allergy Sinus (NDA 21-441) product is similar, the decongestant is not identical and the chlorpheniramine is only 2 mg versus 4 mg in the proposed 3-drug combination. The Sponsor's database and the AERS data are presumptive that the 3 drugs, ibuprofen, phenylephrine, and chlorpheniramine were used concomitantly. The bioequivalence study doses the proposed product to only 41 subjects.

#### 7.4 General Methodology

##### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable to this review.

##### 7.4.1.1 Pooled data vs. individual study data

There was no clinical trial data to pool using the combination product, as only one bioequivalence study was performed (study AD-05-05). The Sponsor pooled the postmarketing adverse event data (from their database and the AERS database) from the original submission of this NDA and the 4-month safety update. No safety signal was found from the pooled data.

#### 7.4.1.2 Combining data

See section 7.4.1.1 above.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for dose dependency for adverse findings

Aside from the single bioequivalence study, AD-05-05, there were no additional studies performed that employed multiple doses.

#### 7.4.2.2 Explorations for time dependency for adverse findings

The Sponsor has not conducted any multiple dose studies with (b) (4) for this application.

#### 7.4.2.3 Explorations for drug-demographic interactions

An insignificantly higher incidence of adverse events was noted among females in study AD-05-05. There were no significant differences in AEs noted by age or race.

#### 7.4.2.4 Explorations for drug-disease interactions

There were no explorations for drug-disease interactions studied for this NDA. The proposed label warns the appropriate risk groups to avoid use of the product or to ask a doctor before use. See sections 9.4 and 10.2 regarding the label.

#### 7.4.2.5 Explorations for drug-drug interactions

The Sponsor conducted studies in this submission (b) (4) to assess any drug-drug interactions between the individual ingredients of the product (ibuprofen, phenylephrine, chlorpheniramine). No clinically significant interactions were noted among the individual ingredients. See section 8.2.

### 7.4.3 Causality Determination

The Sponsor has not performed any special causality assessment. Safety profiles for ibuprofen, phenylephrine, and chlorpheniramine are well characterized. This safety update performed for this

application did not reveal new safety signals for any of the individual ingredients or the combination product.

## **8 ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

There were no new data submitted to this application on dose ranging.

### **8.2 Drug-Drug Interactions**

Phenylephrine is metabolized more rapidly and extensively than pseudoephedrine (Kanfer et al., 1993). The absence of a pharmacokinetic interaction between the three ingredients has been demonstrated in one human study (Wyeth Consumer Healthcare Study AQ-05-05). In the AERS database review (section 7.1.17) there were no cases in either the Suspect, Concomitant or Mixed case cohorts that documented a drug interaction between any combination of ibuprofen, phenylephrine, or chlorpheniramine.

### **8.3 Special Populations**

The proposed label provides the appropriate warnings pertinent to ibuprofen, phenylephrine, and chlorpheniramine. Examples of warnings include: an NSAID (aspirin) allergy alert, stomach bleeding risk, do not use right before or after heart surgery, and with or within 2 weeks of use of a monoamine oxidase inhibitor. Consumers are to ask a doctor before use if they have high blood pressure, glaucoma, or trouble urinating due to an enlarged prostate. The Sponsor has also proposed a new warning that consumers ask a doctor before use if they have asthma. See section 9.4 for a full list of warnings for special populations and all consumers.

### **8.4 Pediatrics**

The Sponsor requested a full waiver of pediatric studies for this drug product stating that:

- it does not represent a meaningful therapeutic benefit over numerous existing treatments for the age range above
- caregivers are likely to select readily available existing treatment products, therefore it is not likely to be used in a substantial number of children
- the dose with respect to both drugs in this product is several times that determined by FDA as safe and effective for children and is therefore unnecessary
- the drug product could be unsafe or inappropriate for children less than 12 years of age.

The proposed dose for this product is one caplet (ibuprofen 200 mg/phenylephrine HCl 10 mg/chlorpheniramine maleate 4 mg) every 4 hours while symptoms persist, with a maximum of 6 caplets in any 24-hour period. This exceeds the approved OTC dose of both ibuprofen and phenylephrine for children less than 12 years of age.

For phenylephrine, for ages 12 and older, the OTC monograph allows a maximum dose of 10 mg every 4 hours (maximum daily dose = 60 mg per 24 hours). For children 2 to 6 years of age, the monograph dose is 2.5 mg every 4 hours (maximum dose 15 mg per 24 hours). For children 6 to 12 years of age, the monograph dose is 5 mg every 4 hours (maximum dose = 30 mg per 24 hours).

There are a variety of cough and cold preparations that contain a combination of pain reliever/fever reducer, nasal decongestant, and/or antihistamine specifically formulated for use in children, some of which are available OTC, however, the marketing of these products could be affected by potential new regulations arising from an Advisory Committee meeting that was held on October 18 and 19, 2007 to discuss the use of cough and cold drugs (including chlorpheniramine, phenylephrine, etc) in pediatric age groups (0 to 6 years) in response to a Citizen Petition. The Committee recommended that cough and cold products should not be used below 2 years of age either as single ingredients or in combination. The Committee recommended assessing the clinical safety and efficacy of ingredients used in cough and cold products, including pharmacokinetic studies in the 2 to under 6 years of age group. The Committee did not address use of cough and cold products in the 6 to under 12 years of age group.

Another Advisory Committee meeting was held on December 14, 2007 to discuss the effectiveness of the current dose of phenylephrine used in OTC cough and cold products in adults. Pediatric age groups were not discussed at this meeting. A Citizen's Petition had challenged the effectiveness of the monograph dose of 10 mg of phenylephrine. The Committee concluded that in adults, there is evidence suggestive that the 10 mg dose is likely to be effective in controlling symptoms of the common cold, but further studies, including PK, PD and clinical studies would be helpful, and that it would also be useful to study the safety and effectiveness of higher doses of phenylephrine. The Sponsor's formulation incorporates the maximum single dose (10 mg) and 24-hour (60 mg) adult dose of phenylephrine.

At this time it is not clear whether a pediatric waiver or deferral will be granted for this application. The Agency is still discussing the whether these products should be labeled for use in the age groups noted above based on extrapolating efficacy from PK studies or whether new studies are required.

## **8.5 Advisory Committee Meeting**

An advisory committee meeting has not been held nor is one scheduled for this application. See section 2.4 and 8.4 regarding advisory committee meetings in October and December 2007 on the safety of cough-cold preparations in children and on the efficacy of single ingredient phenylephrine.

## **8.6 Literature Review**

The Sponsor performed a literature search on the combination of "ibuprofen", "phenylephrine" and "chlorpheniramine" utilizing the following databases: Medline, Biosis Previews, Toxfile,

EMBASE, SciSearch, and Derwent Drug File over the period from 1950 to June 11, 2007. The search did not result in any references concerning the safety of the drug combination.

The Sponsor performed a separate literature search, as requested by FDA, for safety topics related to ibuprofen. The Sponsor cross-referenced to the literature review it performed for NDA 18-989 submitted to FDA on January 31, 2006. The literature contained in the current review is an update to the literature review for NDA 18-989 and covers the period from October 2005 to June 11, 2007. The current search yielded 54 references distributed among the various organ systems, syndromes or subjects, as shown below (n=number of references).

- |                         |                                  |
|-------------------------|----------------------------------|
| Gastrointestinal (n=4)  | Hepatic (n=2)                    |
| Cardiovascular (n=15)   | Allergic (n=4)                   |
| Drug interactions (n=2) | Overdose (n=4)                   |
| Bone/muscle (n=2)       | CNS (n=7)                        |
| General safety (n=2)    | Fertility (n=2)                  |
| Bleeding time (n=3)     | Stevens-Johnson Syndrome (n=1)   |
| Renal (n=4)             | Eye Disorder (n=1)               |
| Cardiovascular (n=15)   | Toxic Epidermal Necrolysis (n=1) |
| Bone/muscle (n=2)       | Drug interactions (n=2)          |
| General safety (n=2)    | Bleeding time (n=3)              |
| Renal (n=4)             |                                  |

The references include epidemiology studies involving ibuprofen emphasizing GI and cardiovascular systems. Clinical trials or other studies in which safety data were summarized are also included in table 8 below. A discussion of the references citing gastrointestinal and cardiovascular adverse events is shown below each adverse event grouping. The remaining adverse event topics (allergic responses, CNS effects, non-GI bleeding adverse events) are less common, so the table entries are followed by a brief comment.

**Table 8. Ibuprofen literature review: safety data**

Author(s), Year	Study Type	Number of Subjects or Subject Age	Treatment/Dose	Results/Comments
<b>Gastrointestinal</b>				
Hippisley-Cox, 2005	Nested case control study in pts age 25 years and older with first dx of upper GI event	9407 incident cases and 88,867 matched controls (median age 68) taken from a database of over 7 million pts		All COX-2 inhibitors and NSAIDs including IBU were associated with a GI event when taken ≤ 90 days prior. The adjusted odds ratio for IBU was 1.42 (95% CI; 1.27-1.59, p<0.001) which was the lowest among all COX-2 inhibitors and NSAIDs included in the analysis.

BEST AVAILABLE COPY

Clinical Review  
Steven Osborne, M.D.

{NDA 22-113}

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

Author(s), Year	Study Type	Number of Subjects or Subject Age	Treatment/Dose	Results/Comments
Moore, 2005	Meta-analysis of 15 R, multiple-dose trials (in short-term and chronic conditions) to compare the GI profile of diclofenac-K with IBU	873 low-dose IBU 247 high-dose IBU 1,297 low-dose diclofenac-K 1,174 high-dose diclofenac-K 1,022 placebo	Low dose IBU = ≤1200 mg/day High-dose IBU = > 1200 mg/day  ≤ 75 mg/ day  > 75 mg/day or placebo	No difference in the incidence of GI events in acute indications between IBU (6.5%, CI=4.5-9.1) and diclofenac-K (6.7%, CI=4.8-9.1). Also no difference with short-term high-dose in chronic conditions or long-term high-dose conditions. Overall for the same indication, duration, and dose category there was no difference in the incidence or relative risk of low-dose diclofenac and ibuprofen for GI events.
Lewis, 2005	Case control study in subjects hospitalized for UGI bleeding who had used OTC and Rx NANSAIDs	359 case subjects and 1889 control subjects	NSAID doses categorized according to FDA approved daily dosage (MDD) for arthritis as low (≤ 0.33% MDD) medium (0.33-0.99% MDD) and high (> 100% MDD)	Among OTC users, 46% of cases and 73% controls reported use < 4 days during the index week. Adjusted odds ratio for UGI toxicity from OTC NSAID use was 0.67(0.43-1.06) for 1-3 days use and 1.83 (1.14-2.95) for 4-7 days of use. For Rx NSAID use the odds ratios were 1.31(0.54-3.18) and 2.57 (1.48-4.45), respectively. No significant difference in the risk of UGI toxicity was observed between OTC IBU and OTC naproxen use (0.84, 95% CI 0.26-2.70). UGI toxicity was dose-related.

Hippesley-Cox et al. (2005, reference 1) describes a nested case-control study in 9407 patients age 25 and older with a first diagnosis of an upper gastrointestinal bleeding event. The study was conducted in 367 general practices in the United Kingdom from August 2000-July 2004. The authors were evaluating whether there was enhanced safety against gastrointestinal events with any of the new cyclo-oxygenase-2 inhibitors compared with non-selective non-steroidal anti-inflammatory drugs. After comparison with the 88,867 matched controls, the adjusted odds ratio for ibuprofen was 1.42 (95% C.I. 1.27-1.59, p<0.001). Compared with adjusted odds ratios for naproxen (2.12, 95% C.I. 1.73-2.58), diclofenac (1.96, C.I. 1.78-2.15), rofecoxib (1.56, C.I. 1.30-1.87), and celecoxib (1.11, C.I. 0.87-1.41), this was the lowest odds ratio for all NSAIDs included in the analysis, except for celecoxib. The authors found no consistent evidence of enhanced safety against gastrointestinal events with any of the new cyclo-oxygenase-2 inhibitors compared with non-selective non-steroidal anti-inflammatory drugs.

Moore 2005 (reference 2) describes a meta-analysis of 15 multiple-dose randomized trials in short-term and chronic conditions to compare the gastrointestinal adverse event profile of diclofenac with ibuprofen. The trials included 873 low dose (≤1200 mg/day) and 247 higher-dose ibuprofen patients, versus 1,297 low dose (≤75 mg/day) and 1,174 higher dose diclofenac patients, in addition to 1,022 placebo patients. He found no difference in GI adverse events with ibuprofen (6.5%, C.I. 4.5-9.1) used for acute indications compared with diclofenac (6.7%, C.I. 4.8-9.1). He also found no difference with chronic use for the same indication, dose category, and duration of use.

Lewis et al. 2005 (reference 3) describes a case-control study in 359 patients hospitalized for upper GI bleeding in 28 hospitals in order to assess the risk of toxicity with OTC non-aspirin NSAIDs (abbreviated NANSAIDs). A total of 1889 control subjects were recruited from the same region.

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg}

Use of OTC NANSAlDs for 4 days during the most recent week had an adjusted odds ratio (OR) of 1.83 (95% confidence interval 1.14-2.95). Use of high-dose OTC NANSAlDs during the index week had an adjusted OR of 5.21 (C.I. 2.32-11.69). In contrast, use of OTC NANSAlDs less than 4 times during the index week (adjusted OR, 0.67; C.I. 0.43-1.06) and use of very low doses of prescription or OTC NANSAlDs during the index week (adjusted OR, 0.74; 95% CI, 0.49-1.12) were not significantly associated with an increased risk of serious gastrointestinal toxicity. The investigators did not observe a significant difference between the risk of toxicity with OTC naproxen versus OTC ibuprofen (adjusted OR, 0.84; 95% CI, 0.26-2.70).

*Comment:*

*The Moore 2005 reference reached a conclusion that ibuprofen, even at OTC doses, does not have a lower incidence of GI adverse events than diclofenac ≤75 mg/day. However, this finding is atypical for OTC doses of ibuprofen. The other two literature references from 2005 shown above (Hippisley-Cox 2005, Lewis 2005) confirm that while ibuprofen use carries some risk of GI adverse events, including bleeding, the risk is possibly the lowest amongst commonly used NSAIDs.*

Author(s), Year	Study Type	Number of Subjects or Subject Age	Treatment/Dose	Results/Comments
<b>Cardiovascular</b>				
Hudson, 2005	Nested case control study in patients with CHF comparing the risk of readmission for CHF between celecoxib and NSAIDS	Pts with CHF ≥ 66 years old, 8,512 cases (readmission for CHF) and 34,048 controls		Cases and controls had similar rates of HTN (35% and 38%, respectively) but cases had more renal disease (23%) than controls (16%). Odds ratio for readmission was similar for celecoxib (reference), IBU (1.17, 0.58-2.34) NAP (1.15, 0.75-1.77) and DIC (1.01, 0.70-1.45), but higher for indomethacin (1.70, 1.06-2.73) and rofecoxib (1.41, 1.21-1.77).
Hudson, 2005	Cohort study of pts with acute MI who were given ASA therapy for secondary prevention to determine whether concomitant IBU increases risk of a second MI	Cohort of 18,503 subjects ≥ 65 years old, 372 of which were dispensed a prescription of IBU.	All NSAIDs IBU NAP DIC	There was a trend to an increased rate of recurrent acute MI in subjects given concomitant ASA and IBU compared to those taking ASA alone as the duration of exposure increased hazard ratios for ever, ≥ 30 days and ≥ 60 days were: 1.01 (95% CI 0.58-1.76), 1.13 (95% CI 0.54—2.39) and 1.83 (95% CI 0.76-4.42), respectively. The authors state, “The results are consistent with data that suggest that regular, but not intermittent, IBU may abrogate the benefits of aspirin when used for the secondary prevention of AML.”

BEST AVAILABLE COPY

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

Author(s), Year	Study Type	Number of Subjects or Subject Age	Treatment/Dose	Results/Comments
Hippisley-Cox, 2005	Case control study to determine risk of MI in patients taking COX-2 inhibitors and NSAIDs	9,218 cases and 86,349 control pts aged 25-100 with first MI.		Subjects taking IBU and DIC within 3 months of the index date had an increased risk for acute MI. Adjusted odds ratio for IBU and NAP were 1.24 (95% CI= 1.11-1.39, p<0.001) and 1.55 (95% CI= 1.39-1.72, P<0.001), respectively. No dosage, frequencies or duration of therapy was noted.
Sheridan, 2005	Observational study to investigate the association of NSAID use and bp in treated hypertensive pts.	A total of 946 pts with a mean age of 68 years. 184 were prescribed NSAIDs.		NSAID usage was not found to be associated with inadequate control of hypertension. For IBU users, the mean SBP was 151(± 16) mm Hg and DBP was 84 (± 9) mm Hg and not significantly different from non-users.
Huerta, 2006	Case control study to determine the risk of first hospitalization for heart failure due to NSAIDs.	A total of 1396 case pts and 5000 controls age 60-84 taken from the UK General Practice Research Database.		The RR for first-time heart failure for IBU was 1.43 (95% CI: 1.01-2.02) whereas for INDO the RR was 3.39 (95% CI: 1.5-7.67). These data included prescription and nonprescription doses of IBU and duration of therapy was not reported for specific NSAIDs.
Kearney, 2006	Meta-analysis of 138 randomized trials involving a comparison between a COX-2 inhibitor and placebo or NSAID for incidence of vascular events.	A total of 145,373 participants.	Doses not specified. Analysis included 112 trials with mean treatment duration of 11 weeks and 9 long-term trials with a mean of 139 weeks.	The summary rate for vascular events (MI, stroke, vascular death) compared with placebo for IBU was 1.51 (95% CI: 0.96-2.37). However duration of treatment and possibly dose was greater than OTC approved use.

Hudson et al. 2005 (reference 4) describes a nested case-control study in a population-based cohort of patients ages  $\geq 66$  years admitted for congestive heart failure (CHF) between January 1998 and March 2003. The magnitude of the risk for congestive heart failure (CHF) through use of individual NSAIDs was not known, but was suspected to be greater than the risk with celecoxib. Four controls were matched to each case on date of cohort entry and time between cohort entry and index date. Exposure was the current use of an NSAID or a COX-2 inhibitor in the 7 days prior to CHF readmission. The investigators calculated the odds of readmission for CHF in patients exposed to naproxen, diclofenac, ibuprofen, indomethacin, or rofecoxib compared with celecoxib, after adjusting for possible confounding variables. They identified 8,512 cases and 34,048 controls. The baseline characteristics between the groups were similar in general. The odds of being readmitted for CHF were higher in patients currently exposed to indomethacin (odds ratio 2.04, 95% confidence interval 1.16-3.58) or rofecoxib (OR 1.58, 95% CI 1.19-2.11) compared with celecoxib. There was no difference between naproxen, diclofenac, and ibuprofen compared with celecoxib, although the numbers of exposed cases and controls were small for these 3 NSAIDs.

Hudson et al. 2005 (reference 5) describes a population based, retrospective cohort study using governmental databases, patients  $\geq 66$  years of age, hospitalized for an acute myocardial infarction between January 1992 and March 1999. The main exposure was the concomitant use of ibuprofen and aspirin after the index acute myocardial infarction. Subjects were followed for one year after the index acute myocardial infarction. A total of 18,503 patients met the study entry criteria. Of these, 372 patients were dispensed a prescription for ibuprofen and 14,424 patients were not dispensed a prescription for any NSAID. There was a trend to an increase in the rate of recurrent

acute myocardial infarction in patients taking ibuprofen and aspirin compared to those taking aspirin alone as the duration of exposure increased [hazard ratios for ever, > or = 30 days, and > or = 60 days exposed were 1.01 (95% CI 0.58-1.76), 1.13 (95% CI 0.54-2.39), and 1.83 (95% CI 0.76-4.42), respectively]. In contrast, subjects taking prolonged naproxen and aspirin had a trend toward a lower rate of recurrent acute myocardial infarction compared to those taking aspirin alone. The authors concluded that regular, but not intermittent, ibuprofen may attenuate the benefits of aspirin when used for secondary prevention of acute myocardial infarction.

Hipsley-Cox et al. (2005, reference 6) describes a nested case-control study in 9218 patients ages 25 and older with a first ever diagnosis of a myocardial infarction. The study was conducted in 367 general practices in the United Kingdom from the year 2000- 2004. The authors were evaluating the comparative risk of myocardial infarction in patients with and without pre-existing coronary heart disease and in those taking and not taking aspirin taking COX-2 inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs). A total of 86,349 controls were matched for age, calendar year, sex, and practice. The odds ratios were adjusted for smoking status, comorbidity, deprivation, and use of statins, aspirin, and antidepressants. The investigators found a significantly increased risk of myocardial infarction associated with current use of ibuprofen (odds ratio 1.24, 95% confidence interval 1.11-1.39). They also found an increased risk with current use of naproxen (OR 1.55 (C.I. 1.39-1.72), rofecoxib (OR 1.32, C.I.1.09-1.61), and diclofenac (OR1.55, C.I. 1.39-1.72). No significant interactions occurred between any of the NSAIDs and either aspirin or coronary heart disease. These results suggest an increased risk of myocardial infarction associated with current use of ibuprofen, naproxen, rofecoxib, and diclofenac. No evidence was found to support a reduction in risk of myocardial infarction associated with current use of naproxen. The authors noted that their study was an observational study and could be subject to residual confounding that cannot be fully corrected for.

Sheridan et al. 2005 (reference 7) describes an observational study in 946 patients, mean age 68 years old, in order to assess the effects of NSAID use on blood pressure. The authors found that in the 184 patients prescribed an NSAID, there was no difference in blood pressure control compared with patients who did not use an NSAID.

Huerta et al. 2006 (reference 8) describes a nested case-control analysis based on the UK General Practice Research Database designed to estimate the risk of a first hospital admission for heart failure associated with the use of non-steroidal anti-inflammatory drugs. The authors identified 1396 cases of first hospital admission for non-fatal heart failure from January 1997 and December 2000, which they compared with a random sample of 5000 controls. The investigators found that the overall risk of a first hospital admission for heart failure associated with current use of NSAIDs was 1.3 (95% CI 1.1 to 1.6) after controlling for major confounding factors. For ibuprofen, the relative risk was 1.43 (95% confidence interval 1.01-2.02), versus 3.39 (C.I. 1.5-7.67) for indomethacin. The authors concluded that the increased risk, although small, may result in considerable public health impact, particularly among the elderly.

Kearney et al. 2006 (reference 9) describes a meta-analysis of data from randomized trials that assess the effects of selective cyclo-oxygenase-2 (COX 2) inhibitors and traditional non-steroidal anti-inflammatory drugs on the risk of vascular events. The authors reviewed sources from

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

Medline and Embase (January 1966 to April 2005); Food and Drug Administration records, and data on file from Novartis, Pfizer, and Merck. Eligible studies were randomized trials that included a comparison of a selective COX 2 inhibitor versus placebo or a selective COX 2 inhibitor versus a traditional NSAID, of at least four weeks' duration, with outcome data on myocardial infarction, stroke, or vascular death. In placebo comparisons, a selective COX 2 inhibitor was associated with a 42% relative increase in the incidence of serious vascular events (1.2%/year v 0.9%/year; rate ratio 1.42, 95% confidence interval 1.13-1.78; P = 0.003), with no significant heterogeneity among the different selective COX 2 inhibitors. The summary rate ratio for vascular events, compared with placebo, was 1.51 (0.96 to 2.37) for ibuprofen, 0.92 (0.67 to 1.26) for naproxen, and 1.63 (1.12 to 2.37) for diclofenac. Selective COX 2 inhibitors were associated with a 42% relative increase in the incidence of serious vascular events (1.2%/year v 0.9%/year; rate ratio 1.42, 95% confidence interval 1.13-1.78; P = 0.003), with no significant heterogeneity among the different selective COX 2 inhibitors.

*Comment:*

*The six references above discussing cardiovascular topics suggest that there might be some increased risk for a cardiovascular event with the use of ibuprofen versus non-use or use of a placebo, but the increase is not large. Most of the studies did not specify the exact of ibuprofen. The proposed label for (b) (4) carries a cardiovascular risk warning. These literature references provide support that the proposed label is adequate to protect potential users from a known, but small cardiovascular risk when the product is used for the requested indications.*

Allergic Reaction				
Author(s), Year	Study Type	Number of Subjects or Subject Age	Treatment/Dose	Results/Comments
Schubert, 2005	Skin prick test followed by a single-blind, placebo-controlled oral NSAID challenge.	260 pts with a diagnosis of NSAID hypersensitivity, mean age 51 years 22.7% atopic disease 21.9% asthma/rhinitis 8.8% chronic urticaria 21.5% infectious disease	50, 100, 200, and 400 mg oral challenge of IBU	In all patients, skin prick tests with NSAIDs were negative.  In total, 606 challenge tests were carried out in the 260 patients. Specifically, ibuprofen was challenged 100 times, and resulted in 10 cutaneous reactions and 2 respiratory reactions.  No anaphylactoid reactions requiring emergency treatment occurred with any NSAID.
Kidon, 2005	Retrospective case series from a pediatric allergy clinic in Singapore. Skin prick test followed by oral provocation.	24 pts over the period March 1, 2003 – February 28, 2004 with diagnosed cross reactive NSAID hypersensitivity (mean age 7.4 years)	Median cumulative reaction-eliciting dose was 7.1 mg/kg	Facial angioedema developed in all pts and generalized urticaria for 38% of pts. 42% of pts had respiratory symptoms with no circulatory compromise. 46% of pts had cross reactive hypersensitivity to acetaminophen.

**BEST AVAILABLE COPY**

*Comment:*

*The two allergy references, Schubert et al 2005 (reference 10) and Kidon et al. 2005 (reference 11) indicate that hyper-sensitivity to ibuprofen may be seen with a potentially higher incidence in patients with other allergy problems, such as atopy, allergic rhinitis, or asthma. The Sponsor's*

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg }

*proposed label includes an NSAID warning. In January 2008 the Sponsor added an asthma warning. Both the NSAID and asthma warning are appropriate.*

Author(s), Year	Study Type	Number of Subjects or Subject Age	Treatment/Dose	Results/Comments
<b>CNS</b>				
<a href="#">Kepa, 2005</a>	Review of 8 patients hospitalized for drug-induced aseptic meningitis (DIAM)	Patient ages ranged from 21-44 years old, 5 males and 3 females		In 3 of the 8 patients, IBU was the suspect drug. The time between drug use and onset of aseptic meningitis was 5, 6, and 7 days. Cause and effect relationship between IBU and DIAM was rated as "Possible" on the Naranjo ADR scale. On the second or third day after hospitalization improvement of symptoms and resolution of CNS disease occurred in all pts.
<a href="#">Chen, 2005</a>	Cohort study to determine whether NSAID use lowers the risk of Parkinson's disease	Cohort of 86,404 men and 97,786 women	IBU ASA Other NSAIDs	A total of 413 incident cases of Parkinson's disease were identified. Overall IBU users had a lower risk for Parkinson's disease than non-users (RR 0.65; 95% CI = 0.48 - 0.89, p = 0.007). No association of Parkinson's disease was seen with ASA use vs. non-users, other NSAIDs or APAP.
<a href="#">Gengo, 2006</a>	R, DB, PC, multi-dose study to determine the effect of IBU on sleep	30 healthy subjects, mean age 28.6 years	IBU 400 mg TID for 3 days or PBO	IBU had no effect on objective and subjective sleep parameters. Mean changes in baseline in sleep efficiency were not different between IBU (0.4±6.3) and PBO (0.3±6.2). Likewise for quality of sleep (8.6±26.8 vs. 3.3±21.3, respectively). No significant mean changes from baseline in subjective sleep scores were noted.

**BEST AVAILABLE COPY**

*Comment:*

*The three references on central nervous system-related topics do not describe any new information on adverse events with ibuprofen use. Kepa et al. 2005 (reference 12) discusses the already-known, rare association between ibuprofen and aseptic meningitis. Chen et al. (reference 13) discusses that users of ibuprofen might have a lower risk of Parkinson's disease. Gengo et al. 2006 (reference 14) found no effect of ibuprofen on sleep.*

<b>Bleeding Time/Blood</b>				
<a href="#">Vicent, 2005</a>	8 year survey of anesthetic and ICU records for the incidence of spinal epidural hematomas	Data from 28,933 patients were analyzed.		During this time period, 4 compressing spinal epidural hematomas were identified. One developed following lumbar epidural analgesia in an orthopedic patient after (concealed) self-administration of high dose of IBU (dose not specified). The patient recovered completely.

*Comment:*

*Vincent et al. 2005 examined the incidence of spinal epidural hematomas over an 8-year period. The sole case involving ibuprofen involved misuse of ibuprofen.*

Overall, this literature review on the safety aspects of ibuprofen was comprehensive and did not reveal adverse events that have not been reported previously.

## 8.7 Postmarketing Risk Management Plan

See section 1.2. The Sponsor should provide the appropriate safety updates per the regulations for an approved NDA.

## 8.8 Other Relevant Materials

None.

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

The Sponsor's bioequivalence study, AD-05-05, adequately characterizes the proposed combination product with ibuprofen 200 mg/phenylephrine 10 mg/chlorpheniramine 4 mg as bioequivalent to the individual ingredients. Under fasted conditions, the combination caplet had an equivalent rate and extent of absorption of ibuprofen, phenylephrine, and chlorpheniramine relative to the single entity marketed products containing ibuprofen (Motrin IB), phenylephrine (Sudafed PE), and chlorpheniramine (Chlor-Trimetron Allergy). Under fed conditions, there was a delay in the Tmax for phenylephrine, but not for ibuprofen or chlorpheniramine. While it is unclear whether the delay in the Tmax for phenylephrine under fed conditions is clinically significant or not, this issue could be addressed in the label if the biopharmaceutics reviewer finds it significant. All three ingredients were well tolerated, whether taken alone or in combination under fasted and fed conditions.

Safety data from the Sponsor's adverse event database, the AERS database, and a literature review support the general safety of ibuprofen in OTC doses. The potential adverse events with use of phenylephrine and chlorpheniramine are well-documented as these are monograph ingredients. Although the proposed 3-drug combination product has not been previously marketed, there is no data to suggest it will not be safe when used as labeled for the requested indications. In contrast, the available data supports the safety of the individual ingredients.

An outstanding issue may be whether PREA is triggered and the product should be developed in a formulation designed for the pediatric age group.

## 9.2 Recommendation on Regulatory Action

The proposed combination of ibuprofen 200 mg/phenylephrine 10 mg/chlorpheniramine 4 mg ( (b) (4) ) has an acceptable safety profile for OTC marketing. While the combination has not been marketed before, the individual ingredients have been marketed for a significant time and extent as an NDA product (ibuprofen) or monograph products (phenylephrine and chlorpheniramine). This product may be approvable in adults; however, this depends upon complete review of CMC, Pharmtox, and Biopharm issues. Restrictions on use in pediatric age

groups may be needed, since the Agency is still discussing whether extrapolating efficacy in younger-than-adult age groups, from data acquired in adult studies, is adequate.

Other outstanding issues at this time that could impact approval of the product are: the biopharmaceutics reviewer's assessment of the bioequivalence study #AD-05-05, the chemistry reviewer's assessment of the dissolution study linking the current formulation with the formulation used in study #AD-05-05, the status of the phenylephrine degradant (b) (4) and the pharmacology-toxicology reviewer's assessment of the rat toxicology study with the degradant, (b) (4).

### **9.3 Recommendation on Postmarketing Actions**

No postmarketing actions are recommended for this product.

#### **9.3.1 Risk Management Activity**

No special post-marketing risk management activities are recommended.

#### **9.3.2 Required Phase 4 Commitments**

No special Phase 4 commitment is recommended.

#### **9.3.3 Other Phase 4 Requests**

None.

### **9.4 Labeling Review**

The proposed Drug Facts label and carton appearance for the 10-count blister pack product are shown on the next two pages. The Drug Facts label and the appearance of the 20-count carton are the same as for the 10-count carton (except that 20 caplets are in the carton). The essential elements of the Drug Facts label are present in the labels of the 10-count blister pack and 20-count carton. The directions for use and the appropriate warnings for the individual ingredients, ibuprofen, phenylephrine, and chlorpheniramine, appear to be appropriate. However, an interdisciplinary scientist from the Division of Nonprescription Regulatory Development will review the label for proper format and any deficiencies. It is acceptable from a clinical point of view. The label should state a maximum of 7 days of use to be consistent with the monograph limit of 7 days of use for phenylephrine. Also, the label should state do not use if less than 12 years of age.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 9.5 Comments to Applicant

None.

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

The only study included in this submission, bioequivalence study AD-05-05, was reviewed earlier in this review.

### 10.2 Line-by-Line Labeling Review

An interdisciplinary scientist from the Division of Nonprescription Regulatory Development is reviewing the proposed label for this product.

The label should convey that the product is indicated for temporary relief of symptoms associated with hay fever or other respiratory allergies, and the common cold but should not exceed use for up to (b) (4) consecutive days for pain, up to 7 consecutive days for the treatment of nasal congestion, and up to 3 consecutive days for the treatment of fever. To be consistent with the monograph limit of 7 days of use for phenylephrine the label should state a maximum of 7 days of use. Also, the label should state do not use if less than 12 years of age.

#### *Comment:*

*On January 31, 2008 the Sponsor submitted a request to add a new asthma warning to the label. The previous proposed labeling contains an Allergy Alert warning, which states that ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin and that symptoms may include asthma (wheezing). The new warning would add a bullet advising consumers to ask a doctor before use if you have asthma, as shown below in a side-by-side comparison of the previously-proposed label and the newly proposed label (see next page). This warning appears reasonable.*

Clinical Review  
Steven Osborne, M.D.  
{NDA 22-113}

{ (b) (4) ibuprofen 200 mg, phenylephrine 10 mg, chlorpheniramine 4 mg}

---

(b) (4)



## REFERENCES

1. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005; 331(7528):1310-1316.
2. Moore N. Gastrointestinal (GI) safety of low dose diclofenac-potassium compared to low dose ibuprofen. *Pharmacology* 2005; 75:195-212.
3. Lewis JD, Kimmel SE, Localio AR, Metz DC, Farrar JT, Nessel L et al. Risk of serious upper gastrointestinal toxicity with over-the-counter nonaspirin nonsteroidal anti-inflammatory drugs. *Gastroenterology* 2005; 129(6):1865-1874.
4. Hudson M, Rahme E, Richard H, Pilote L. The risk of congestive heart failure with non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors- a class effect? *Arthritis Rheum* 2005; 52: S402.
5. Hudson M, Baron M, Rahme E, Pilote L. Ibuprofen may abrogate the benefits of aspirin when used for secondary prevention of myocardial infarction. *J Rheumatol* 2005; 32(8):1589-1593.
6. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005; 330(7504):1366.
7. Sheridan R, Montgomery AA, Fahey T. NSAID use and BP in treated hypertensives: a retrospective controlled observational study. *J Hum Hypertens* 2005; 19(6):445- 450.
8. Huerta C, Varas-Lorenzo C, Castellsague J, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. *Heart* 2006.
9. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; 332(7553):1302-1308.
10. Schubert B, Grosse Perdekamp MT, Pfeuffer P, Raith P, Brocker EB, Trautmann A. Nonsteroidal anti-inflammatory drug hypersensitivity: fable or reality? *Eur J Dermatol* 2005; 15(3):164-167.
11. Kidon MI, Kang LW, Chin CW, Hoon LS, See Y, Goh A et al. Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children. *Pediatrics* 2005; 116(5):e675-e680.

12. Kępa L, Oczko-Grzesik B, Stolarz W, Sobala-Szczygiel B. Drug-induced aseptic meningitis in suspected central nervous system infections. *J Clin Neurosci* 2005; 12(5):562-564.

13. Chen H, Jacobs E, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. *Ann Neurol* 2005; 58(6):963-967.

14. Gengo F. Effects of ibuprofen on sleep quality as measured using polysomnography and subjective measures in healthy adults. *Clin Ther* 2006; 28(11):1820-6.

15. Vicent O, Groble R, Wiessner D, Heller A, Koch T, Ritz R. The incidence of compressing spinal epidural haematomas during central neuraxial block performance. An 8-year survey. *Reg Anesth Pain Med* 2005; 30:53.

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

/s/

-----  
Steven Osborne  
3/14/2008 01:12:39 PM  
MEDICAL OFFICER

Bindi Nikhar  
3/14/2008 01:35:02 PM  
MEDICAL OFFICER

Review incomplete as Dr. Osborne is leaving the division.  
Approval of this product will depend upon outstanding  
clinical and non-clinical issues mentioned in this review.  
Dr. Linda Hu's medical review will cover these  
issues. I will be writing a TL memo.



	Content Parameter	Yes	No	NA	Comment
<b>EFFICACY</b>					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 AD-05-05 Indication: temporary relief of symptoms of hay fever, respiratory allergies, and common cold  Pivotal Study #2 Indication:	X			One bioequivalence study (AD-05-05) was conducted. One dissolution study was done comparing the current formulation with that used in study #AD-05-05
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Agency agreed with one BE study fed + fasted comparing combination with individual ingredients
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	The proposed combination is currently not marketed anywhere in the world, per the sponsor.
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X*			*Applicant did not submit full drug-drug interaction information (effect of ibuprofen on phenylephrine)
19.	Has the applicant submitted adequate information to assess the arrhythmia potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			See #17 above. Safety data submitted on use of individual ingredients. Some data may refer to concomitant use.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>2</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	Indicated for intermittent use.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

<sup>2</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
23.	Has the sponsor submitted the coding dictionary <sup>3</sup> used for mapping investigator verbatim terms to preferred terms?		X		This information is not needed for this review.
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	There were no deaths. A summary was submitted for the one dropout in Study AD-05-05 (blood draw difficulty).
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested for <12 years of age. Not a filing issue, but PREA issues will need to be addressed in review.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			This product has been developed substituting phenylephrine for pseudoephedrine in response to the abuse of phenylephrine.
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

<sup>3</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
<b>CONCLUSION</b>					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Steven Osborne, M.D.

November 16, 2007

Reviewing Medical Officer

Date

Bindi Nikhar, M.D.

November 16, 2007

Clinical Team Leader

Date

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

/s/

-----  
Steven Osborne  
11/19/2007 07:56:42 AM  
MEDICAL OFFICER  
corrected clinical filing checklist [REDACTED] (b) (4) (stamp  
date, 505b2)

Bindi Nikhar  
11/19/2007 12:54:41 PM  
MEDICAL OFFICER



	Content Parameter	Yes	No	NA	Comment
<b>EFFICACY</b>					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 AD-05-05 Indication: temporary relief of symptoms of hay fever, respiratory allergies, and common cold  Pivotal Study #2 Indication:	X			One bioequivalence study (AD-05-05) was conducted. One dissolution study was done comparing the current formulation with that used in study #AD-05-05
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Agency agreed with one BE study fed + fasted comparing combination with individual ingredients
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	The proposed combination is currently not marketed anywhere in the world, per the sponsor.
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X*			*Applicant did not submit full drug-drug interaction information (effect of ibuprofen on phenylephrine)
19.	Has the applicant submitted adequate information to assess the arrhythmia potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			See #17 above. Safety data submitted on use of individual ingredients. Some data may refer to concomitant use.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>2</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	Indicated for intermittent use.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

<sup>2</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
23.	Has the sponsor submitted the coding dictionary <sup>3</sup> used for mapping investigator verbatim terms to preferred terms?		X		This information is not needed for this review.
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	There were no deaths. A summary was submitted for the one dropout in Study AD-05-05 (blood draw difficulty).
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested for <12 years of age. Not a filing issue, but PREA issues will need to be addressed in review.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			This product has been developed substituting phenylephrine for pseudoephedrine in response to the abuse of phenylephrine.
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

<sup>3</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
<b>CONCLUSION</b>					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Steven Osborne, M.D.  
 \_\_\_\_\_  
 Reviewing Medical Officer

November 16, 2007  
 \_\_\_\_\_  
 Date

Bindi Nikhar, M.D.  
 \_\_\_\_\_  
 Clinical Team Leader

November 16, 2007  
 \_\_\_\_\_  
 Date

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

/s/

-----  
Steven Osborne  
11/16/2007 10:20:27 AM  
MEDICAL OFFICER

Bindi Nikhar  
11/16/2007 01:32:20 PM  
MEDICAL OFFICER