

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022113Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 30, 2011
From	Daiva Shetty, MD
Subject	Cross-Discipline Team Leader Review
NDA#	22-113
Applicant	Pfizer Consumer Healthcare
Date of Submission	June 21, 2011
PDUFA Goal Date	December 21, 2011
Proprietary Name / Established (USAN) names	Advil Allergy & Congestion Relief
Dosage forms / Strength	Ibuprofen 200 mg/Phenylephrine HCl 10 mg/ Chlorpheniramine maleate 4 mg Tablet
Proposed Indication(s)	<ul style="list-style-type: none">• Temporary relieves these 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• Reduces swelling of the nasal passages• Temporary restores freer breathing through the nose
Recommended:	Approval pending satisfactory results of the manufacturing facility inspection

1. Introduction

This NDA proposes a new combination, Ibuprofen (IBU) 200 mg, Phenylephrine Hydrochloride (PE) 10 mg, Chlorpheniramine maleate (CHLOR) 4 mg, tablet for over-the-counter marketing.

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 (PSE) containing drug products over the counter.

2. Background

This is the second review cycle for this NDA. The original NDA for this product was submitted by Wyeth Consumer Healthcare (former sponsor of this NDA) on September 25, 2007. 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 [REDACTED] (b) (4), it was revealed that there were major flaws in the analytical assay that quantified the total PE (unmetabolized PE plus PE converted back from conjugated PE

metabolites). Based on this flawed assay, results from the pivotal bioequivalence study could not be considered acceptable to support approval of NDA 22-113.

The Complete Response letter issued on July 25, 2008 listed the following four deficiencies:

1. The submitted PK data for phenylephrine are not reliable due to major flaws in the analytical assay methodology. Further, any differences noted between the original and repeat results between samples within a subject, were 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 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 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. Then, you have the option of either 1) reanalyzing the stored PK samples from study AD-05-05, provided stability of these samples can be assured or 2) conducting an entirely new PK study identical in design to study AD-05-05 with the to be marketed caplet formulation of IBU/PE/CHLOR. We recommend that you analyze the PK samples (stored or newly acquired) using the newly validated analytical method for PE. 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.

2. We note that the qualifying study for the phenylephrine succinate 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.

3. In addition, we have the following labeling comments:

- 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”, we agree with the inclusion of the term “asthma.”
- c. Under the “Do not use” subsection of Warnings, we agree with adding the bulleted statement “in children under 12 years of age”. In addition, under Directions, we agree

with changing the statement [REDACTED] (b) (4) to read
“children under 12 years of age: do not use”.

These are preliminary labeling comments. Further labeling recommendations are expected based on our review of the data in the next review cycle.

4. 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.

3. CMC/Device

There is no CMC review for this submission at the time of this review. The only outstanding issue is the cGMP inspection of the manufacturing site. This NDA should not be approved until Offices of Compliance and New Drug Quality Assessment have determined the facility inspection to be acceptable.

4. Nonclinical Pharmacology/Toxicology

Please refer to Dr. Wafa Harrouk’s Review entered in DARRTS on 10/28/2011.

In this “Complete Response” submitted on June 26, 2011, the sponsor has addressed the deficiencies listed in the 2008 action letter which include conducting a 90-day repeat dose toxicity and toxicokinetics study with the degradant [REDACTED] (b) (4)

[REDACTED] (b) (4) was identified as a degradant in stability samples in the original NDA submission and whose levels were found to be above the allowed 0.5% impurity relative to phenylephrine based on the ICH Q3B guidance determination. In the original NDA, [REDACTED] (b) (4) underwent a qualification program consisting of two genotoxicity studies and a 2-week repeat-dose general toxicity study. Due to the potential chronic use of the product for the allergy indication sought under this NDA, the Division recommended that a 90-day repeat dose toxicity and toxicokinetics study [REDACTED] (b) (4) be conducted in the second review cycle.

[REDACTED] (b) (4) has shown no evidence of genotoxicity in the Ames Salmonella histidine reversion or the human chromosome aberration assays. Similarly, no evidence of toxicity was seen in a 2-week repeat dose toxicity study which was conducted with [REDACTED] (b) (4) in the original NDA review cycle. In this submission, [REDACTED] (b) (4) showed no evidence of toxicity in the 90-day repeat dose toxicity. Based on the above information, Dr. Harrouk concluded that [REDACTED] (b) (4) is considered to be qualified at concentrations up to [REDACTED] (b) (4) in the proposed drug formulation.

Nonclinical safety issues relevant to clinical use: None

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Partha Roy's review completed on November 16, 2011.

Pfizer conducted a new PK trial AD-08-10, as requested in the 2008 action letter titled "A Four-Way Crossover, Bioavailability Study of a Caplet Formulation Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg and Chlorpheniramine Maleate 4 mg." This study investigated ibuprofen drug interaction, formulation effects and foods effects. A new and validated assay that measures free PE was employed in this study. This revised and revalidated assay specifically measures free PE in the sample as opposed to the total PE assay that was used in study AD-05-05 in the original submission. This new method was judged to be adequately validated to measure free PE in a previous review of Advil Congestion Relief dated 01/14/2010 by Drs. Ying Fan and Atul Bhattaram under NDA 22-565 (ibuprofen and phenylephrine tablet; approved on 05/27/2010).

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 4 mg) single entity products administered concomitantly and to Motrin IB (IBU 200 mg) administered alone. Additionally, in the same study, the rate and extent of IBU, PE and CHLOR absorption from IBU/PE/CHLOR formulation was measured under fed condition to evaluate the food effect, if any (comparison of fasted vs. fed condition).

Under fasted conditions, the IBU/PE/CHLOR caplet was equivalent in systemic exposure to the monoproducts administered together for all three ingredients of IBU, PE and CHLOR as 90% CIs around the ratios for AUC_t, AUC_{inf} and C_{max} were all within the 80-125% limits for bioequivalence.

No food effect was reported for CHLOR with respect to AUC and C_{max}. While both IBU and PE was equivalent for AUC under fasted versus fed conditions, a food effect was observed for C_{max} with IBU and PE. Under fed state, IBU and PE C_{max} values decreased by 18% and 23%, respectively compared to fasted state. In the first cycle of submission for the current NDA, study AD-05-05 reported a lack of food effect for IBU [ratio (90% CI) of 90.21 (81.72 - 99.58)]. In addition, Advil Congestion Relief also showed a similar observation of marginal food effect for IBU [ratio (90% CI) of 87.6 (79.8 - 96.1)] which was attributed to the IBU component only and not to its co-administration with other active ingredients. Similar to this product, Advil Congestion Relief also showed a food effect of 22% decrease in C_{max} for PE. Based on the observations above, a lack of clinically significant food effect can be concluded for all three active ingredients for the triple combination product of IBU/PE/CHLOR. In the proposed label consistent with other IBU containing drug products, patients are directed to take the drug product with food or milk if stomach upset occurs. This statement is supported by the conclusion of lack of significant food effect for all three active ingredients. The same language appears on Advil Congestion Relief label.

Under fasted state, the median IBU T_{max} for the IBU/PE/CHLOR caplet was 15 minutes and 29.5 minutes longer than that for Motrin IB + Sudafed PE + Chlor- Trimeton (120 vs. 105

minutes) and Motrin IB tablets alone (120 vs. 90.5 min), respectively. This data is consistent with the previous findings from the original submission. Food had no effect on Tmax of the combination caplet.

The sponsor provided Tmax values as well as efficacy data from previous NDAs associated with approved IBU containing drug products. The data clearly demonstrated that products with longer Tmax (110-131 minutes) similar to the IBU/PE/CHLOR caplet (Tmax: 120 min) were significantly efficacious for the IBU component compared to placebo. These historical data, taken together, provided adequate evidence to conclude that prolongation of Tmax to 120 minutes would not have any significant impact on the IBU-dependent efficacy of the triple combination product of IBU/PE/CHLOR.

The sponsor also developed a PK/PD model for IBU in dental pain that could characterize PK profiles of different formulations, establish IBU exposure-response relationships for pain relief or remedication, and create PK nomograms to evaluate the effect of IBU formulations on time to meaningful pain relief (TMPR) and time to first perceptible pain relief (TFPR) and time to remedication (REMD) to support the efficacy of IBU containing drug products with prolonged Tmax values. It was concluded that 30 minute difference in median Tmax did not appear to translate into major differences in pain relief score.

Lack of clinically relevant drug-drug interactions between these three active components are addressed by the following taken together: 1) lack of interaction between CHLOR and PE per OTC Cold and Cough monograph for Over-The-Counter Human Use (21 CFR 341), 2) lack of interaction between IBU and CHLOR per approval of Advil Allergy Sinus Caplets (triple combination of ibuprofen, pseudoephedrine and chlorpheniramine), and 3) lack of interaction between IBU and PE per approval of Advil Congestion Relief (double combination of ibuprofen and phenylephrine).

Division of Bioequivalence and GLP Compliance (DBGC) in the Office of Scientific Investigations (OSI) conducted inspections of the clinical and analytical portions of the bioequivalence study AD-08-10. The clinical portions of the study were conducted at

(b) (4)

An inspection was conducted at the site from July 21 through October 18, 2011. Following the inspection, no Form FDA-483 was issued for this study. The analytical portions of the study were conducted at (b) (4). Following the inspection, no Form FDA-483 was issued. Following the above inspections, OSI recommended that the data for the clinical and analytical portions of study AD-08-10 may be accepted for Agency review.

Dr. Partha Roy recommended an Approval action. There are no notable outstanding clinical pharmacology issues.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There is no clinical efficacy review for this application. No new controlled clinical efficacy and safety studies were conducted for NDA 22-113; this NDA relies on the bioequivalence program.

There are no notable unresolved efficacy issues.

8. Safety

Please refer to the Clinical review by Dr. Linda Hu entered in DARRTS on November 17, 2011.

The proposed fixed-combination drug product has never been marketed worldwide. However, all three ingredients in the Advil Allergy & Congestion Relief tablet, i.e. phenylephrine, chlorpheniramine, and ibuprofen have a long marketing history for OTC use; IBU since 1984, PE since the early 1960s and CHLOR for more than 40 years.

There were no safety issues identified during the first review cycle. The complete response to the 2008 action letter included a Safety Update derived from a combined review of postmarketing adverse event (AE) databases, literature and the three clinical pharmacology studies supporting the NDA. These were the single-dose, crossover studies AD-05-05, AD-06-06, and AD-08-10 which enrolled a total of 139 subjects.

No deaths or nonfatal serious adverse events (AEs) were reported during three clinical pharmacology studies. Headache, dizziness, and nausea were the most common adverse events reported.

The Sponsor submitted a safety update using two safety databases: AERS (covering the period July 1, 2007 – March 31, 2010) and their own database (covering October 1, 2007 – January 1, 2011). Since this fixed-combination drug product has never been marketed anywhere in the world, the Sponsor searched the two databases for cases with mentions of all three active ingredients. A total of 11 serious adverse events were identified; none of them can be directly linked to the use of the three ingredients in the proposed product. The postmarketing cases were confounded by the concomitant use of other medications or the presence of underlying serious medical conditions.

This submission included an update of safety from the literature 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. The literature reports are consistent with already known safety profiles of each active ingredient. No new safety issues were identified.

There are no notable outstanding safety issues. The drug should be approved based on its safety profile.

9. Advisory Committee Meeting

No Advisory Committee was held for this particular application.

10. Pediatrics

For children under the age of 12 the Sponsor proposed 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 also requested a deferral of studies for those aged 2 to 11 years and a waiver for those aged 0 to < 2 years since FDA has stated that over-the-counter cough and cold medicines in infants and children under age 2 should not be used because serious and potentially life-threatening side effects may occur.

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. The Sponsor has performed PK modeling analyses in order to determine if a common dose and dosing interval can be identified, that can provide pediatric exposures comparable to adult exposures for all 3 ingredients. The Sponsor's initial plan for pediatric studies included single and multiple dose pharmacokinetic studies in (b) (4)

. DNCE found this proposal unacceptable and recommended an alternative plan:

- 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.

These issues have been presented to the Pediatric Review Committee (PeRC) on September 14, 2011. PeRC agreed with the waiver for 0-2 years and labeling the product for those 12 years and older; however, PeRC disagreed with the plan for studies in the 2-11 y/o age group. The committee thought it unsafe to study this triple combination product in children until substantial safety and efficacy data become available for each single ingredient. This was conveyed to the sponsor. A new, revised pediatric plan has been submitted by the Sponsor on November 23, 2011 and has been forwarded to PeRC. At the time of this review, assessment on the acceptability of this new proposal by PeRC is pending.

11. Other Relevant Regulatory Issues

The Sponsor submitted Form 3454 that the investigators lacked any significant financial interest in this product or significant equity in the Sponsor. DSI audit has been completed and found both clinical as well as analytical portions of study AD-08-10 to be acceptable.

The only unresolved regulatory issue remains the cGMP inspection of the manufacturing site.

12. Labeling

The Sponsor is proposing to market 10-, 20-, 40-, 50-count cartons, 10-count blister, and 1-count pouch shelf keeping units. Labeling reviews have been conducted by Dr. Ayana Rowley from the Division of Nonprescription Regulation Development (see her review entered in DARRTS on 11/29/2011) and by Dr. Lissa Owens from the Division of Medication Error Prevention and Analysis (DMEPA) (see her review entered in DARRTS on 11/8/20). Labeling recommendations listed in the 2008 action letter have been addressed. Additional recommendations from both teams on minor labeling changes were negotiated and agreed with the sponsor. The proposed label contains all standard warnings for all the three active ingredients.

The proposed proprietary name, Advil Allergy & Congestion Relief, has been reviewed by DMEPA and was found to be acceptable (see letter to the sponsor dated 9/16/2011).

The final printed label has not been submitted by the sponsor at the time of this review.

There are no outstanding labeling issues.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend an Approval regulatory action pending satisfactory results of the manufacturing facility inspection.

- Risk Benefit Assessment

The new proposed IBU/CHLOR/PE combination product has a favorable safety profile for OTC marketing.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

Pediatric clinical safety, efficacy, and pharmacokinetic studies will be requested for the 2 to 11 years age population as a PMR under PREA. Final recommendations by PeRC for these studies are pending at this time.

- Recommended Comments to Applicant

None.

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

/s/

DAIVA SHETTY
12/02/2011