

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022113Orig1s000**

**SUMMARY REVIEW**

## Summary basis for Regulatory Action

<b>Date</b>	12/20/11
<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>	Advil Allergy and Congestion Relief Chlorpheniramine 4 mg, ibuprofen 200 mg, phenylephrine 10 mg
<b>Dosage Forms / Strength</b>	tablet
<b>Proposed Indication(s)</b>	Relief of symptoms associated with hay fever or other respiratory allergies, or the common cold
<b>Action:</b>	<i>approval</i>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Linda Hu
Statistical Review	
Pharmacology Toxicology Review	Wafa Harrouk/Paul Brown
CMC Review/OBP Review	Swapan De
Microbiology Review	
Clinical Pharmacology Review	Partha Roy/Suresh Doddapaneni
DDMAC	
DSI	Michael Skelly
CDTL Review	Daiva Shetty
OSE/DMEPA	Lissa Owens/Carlos Mena-Grillasca
OSE/DDRE	
OSE/DSRCS	
Other (labeling)	Ayana Rowley/Elaine Abraham

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, Pfizer Consumer Healthcare (formerly Wyeth Consumer Healthcare) has submitted NDA 22,113 as a 505(b)(2) application for their over-the-counter (OTC) combination drug product, Advil Allergy and Congestion Relief. 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 tablet every 4 hours while symptoms persist.

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

During the first review cycle a number of deficiencies were noted for which the applicant received a complete response letter on July 25, 2008. Below are listed those 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  $T_{max}$  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. 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 (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.*

*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 (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.*

The applicant has now submitted a complete response to these deficiencies which is the subject of this review.

### **3. CMC/Microbiology/Device**

There are no unresolved chemistry issues.

The CMC reviewer concluded 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) (the original name) over the proposed shelf life (18 months) when stored as labeled; labeling has been found acceptable.*

However, the CMC reviewer previously recommended an Approvable action pending final facilities inspection and approval that demonstrates the applicant is fully in compliance with cGMP requirements.

Dr. Swapan De now comments: The pending EER issue for the chemistry, manufacturing and controls for NDA 22-113 is resolved on December 4, 2011 and it is acceptable.

I agree. For additional details, please refer to the CMC review by Dr. Swapan De and previous CMC reviews.

### **4. Nonclinical Pharmacology/Toxicology**

Dr. Harrouk previously provided the following conclusions (excerpted from her original 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.*

For this review cycle the applicant submitted the results of a 90 day study in rats. (b) (4) showed no evidence of toxicity in the 90-day repeat dose toxicity study which was conducted at concentration up to (b) (4). Based on this, Dr. Harrouk comments that (b) (4) is considered qualified at concentration up to (b) (4) in the proposed formulation.

I agree with Dr. Harrouk.

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

### **5.1. Notable issues**

Pfizer conducted a new PK trial AD-08.

The following is excerpted from Dr. Roy's review:

*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).*

#### *Relative Bioavailability under fasted state*

*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<sub>t</sub>, AUC<sub>inf</sub> and C<sub>max</sub> were all within the 80-125% limits for bioequivalence.*

#### *Food Effect*

*Based on the observations above (not included here), 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,*

*the 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.*

#### *Delayed Tmax for IBU*

*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 products were shown to provide acceptable onset of pain relief, fever reduction and onset of sleep. In addition, the infrequent use of rescue medication within the first two hours of taking these medications further indicates that subjects were receiving adequate pain relief. Some of these IBU-containing products also showed efficacy comparable to reference IBU-containing products with much shorter Tmax but comparable systemic exposure within their respective NDAs. 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.*

*In addition to above, 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. The same model had been submitted to support Advil Congestion Relief. Simulations were conducted to evaluate the impact of 30 minute delay (1.5 hr vs. 2 hr) in Tmax between single-ingredient IBU product and the double combination (IBU/PE) on pain relief. It was concluded that 30 minute difference in median Tmax, which is also the case in this application, did not appear to translate into major differences in pain relief score.*

The 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. Following the inspection, no Form FDA-483 was issued for any site. 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. I agree with this recommendation. The applicant has addressed the PK, food effect and delayed Tmax issues adequately. The reader is referred to Dr. Roy's review for details of the studies. There are no outstanding clinical pharmacology issues.

## **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, (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.

#### 7.3.2. Post-marketing safety

#### **Safety Conclusions:**

The reader is referred to my previous review for this NDA and to the medical officer (Dr. Hu) and CDTL (Dr. Shetty) reviews for details of the safety review.

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.

Since this fixed-combination drug product has never been marketed anywhere in the world, the applicant searched two databases for cases with mentions of all three active ingredients. A total of 11 serious adverse events were identified which were confounded by the concomitant use of other medications or the presence of underlying serious medical conditions.

This submission also 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. The literature reports are consistent with already known safety profiles of each active ingredient.

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. No new safety issues are identified.

The proposed label conveys appropriate warnings. The label will have to limit duration of use for 7 days in keeping with the monograph limit of duration of use for phenylephrine.

The reader is referred to the reviews by Drs. Hu and Shetty 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. Based on the monograph allowed dosing for phenylephrine and chlorpheniramine and based on efficacy and safety data from an approved NDA for ibuprofen, it is appropriate to label this product down to the age of 12. This was discussed at a PeRC meeting and there was agreement with this approach. Furthermore, it was also agreed that 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. However, the applicant will need to develop an age appropriate formulation for this product for children down to 2 years of age especially if the applicant determines that higher than monograph dosing for phenylephrine is needed to match the dosing interval of ibuprofen and chlorpheniramine. Further, chlorpheniramine does not have a cold indication in a final monograph. However, the committee thought that it is unsafe to study this triple combination product in children until substantial safety and efficacy data is available for each single ingredient. This was conveyed to the sponsor.

The following was sent to the applicant:

### 1-PK Studies

You must conduct PK trial(s) in children 6 to < 12 who may benefit from the drug (i.e. not in otherwise healthy pediatric volunteers). You should conduct single and multiple dose PK trial(s) that would evaluate the appropriate dosing interval based on pharmacokinetics, safety, and tolerability of phenylephrine in children, and in order to identify whether the dosing interval for phenylephrine can overlap with that of ibuprofen and chlorpheniramine. After you identify the phenylephrine dose, develop and use an age appropriate triple ingredient formulation in the described studies. Any new commercially marketable formulation you develop for use in children must meet FDA standards for marketing approval. You should also provide single and multiple dose PK information for chlorpheniramine in this pediatric age group.

Final Protocol Submissions: December 2012

Final Study Report Submission: December 2013

### 2-Efficacy and Safety Trials

You must conduct randomized, double blind, placebo controlled clinical safety and efficacy trial(s) in children 6 to < 12 years of age to evaluate PD response and clinical symptoms response of phenylephrine, chlorpheniramine, and the triple combination for the temporary relief of nasal congestion and other symptoms associated with the common cold. The trial(s) should evaluate clinical efficacy as well as safety of phenylephrine, chlorpheniramine, and the triple combination in this population, obtain data to support the appropriate dosing interval, and allow dosing to cover the expected period of clinical use (for example, up to 7 days). The study(ies) must include adequate representation of these age groups and be conducted in the target population, i.e. children with cough and cold symptoms.

Final Protocol Submission: June 2013

Final Study Report Submission: June 2015

### 3 –PK Studies

You must conduct PK trial(s) in children 2 to < 6 who may benefit from the drug (i.e. not in otherwise healthy pediatric volunteers). You should conduct single and multiple dose, PK trial(s) that would evaluate the appropriate dosing interval based on pharmacokinetics, safety, and tolerability of phenylephrine in children, and in order to identify whether the dosing interval for phenylephrine can overlap with that of ibuprofen and chlorpheniramine. After you identify the phenylephrine dose, develop and use an age appropriate triple ingredient formulation in the described studies. Any new commercially marketable formulation you develop for use in children must meet FDA standards for marketing approval. You should also conduct a relative bioavailability study in adults to evaluate the new pediatric formulation compared to the adult formulation. You should also provide single and multiple dose, PK information for chlorpheniramine in this pediatric age group.

Final Protocol Submission: December 2015

Final Study Report Submission: December 2016

### 4—Efficacy and Safety Trials

You must conduct randomized, double blind, placebo controlled clinical safety and efficacy trial(s) in children 2 to < 6 years of age to evaluate PD response and clinical symptoms response of phenylephrine, chlorpheniramine, and the triple combination for the temporary relief of nasal congestion and other symptoms associated with the common cold. The trial(s) should evaluate clinical efficacy as well as safety of phenylephrine, chlorpheniramine, and the triple combination in this population, obtain data to support the appropriate dosing interval, and allow dosing to cover the expected period of clinical use (for example, up to 7 days). The study(ies) must include adequate representation of these age groups and be conducted in the target population, i.e. children with cough and cold symptoms.

Final Protocol Submission: May 2017

Final Study Report Submission: August 2019

A new revised pediatric plan was submitted to the Division by the applicant on November 23, 2011 and reviewed by PeRC. They had no objections to the revised pediatric plan. The only issue was that the applicant did not feel that a relative bioavailability study in adults was warranted because PK, efficacy and safety studies were being performed in children and the drug would be indicated in children. This was discussed with Dr. Roy who provided the following comments to me in an e-mail:

*I had a discussion with Suresh this morning. He is in agreement with all that we discussed; why we would need a relative BA study in a typical pediatric drug development. Having said that, this particular case is somewhat unique in the sense that we are requiring the sponsor to collect PK, efficacy and safety data in the pediatric population. Suresh pointed out and I agree that if this particular formulation is only meant to be used by the pediatric population and not by adults, meaning it will be a distinct product (separate from the adult product) with its own separate label, then such relative BA information is not required. Although such info. may be informative for the sponsor to optimize their own drug development, however it is really their choice.*

*If the above assumption is reasonable, then we can certainly agree to the sponsor's proposal of not conducting the relative BA trial.*

The applicant intends to study a dose of phenylephrine for the childrens product that will contain a higher concentration of phenylephrine than is approved in the monograph. Therefore, if a product is developed with a higher than monograph dose of PE, this product will only be appropriate for children (in whom it will be studied). Therefore I agree that relative bioavailability studies in adults are not needed at this time and can be performed if and when the applicant chooses to pursue adult use of this product.

## **10. Financial Disclosure**

No issues were identified.

## 11. Labeling

The reader is referred to the review by Ayana Rowley for details of the label review. Only 2 issues will be discussed here.

First, the applicant has used both the term (b) (4) and also the term “tablet” on the principal display panel (PDP). Although there is an inconsistency in the terminology presented, the term (b) (4) is commonly used to convey to the consumer a variety of dosage forms (tablet, capsule, etc) and the term exists on other nonprescription products. No evidence has been provided that this inconsistency has led to consumer confusion or has resulted in any serious adverse events. Therefore, we will allow the term (b) (4) on the PDP.

Second, there was discussion as to whether we should highlight the active ingredient “phenylephrine” on the outer carton PDP and immediate container blister to distinguish the product from Advil Allergy Sinus in which the ingredients only differ by the decongestant. However, there are no regulatory requirements to highlight specific active ingredients and there is no specific safety issue that would otherwise suggest that this needs to be done. It is possible that highlighting one ingredient could have the unintended consequence of diminishing the consumer’s recognition of the other ingredients in the product. Therefore at this time, the decision is to not highlight any 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).

There are no outstanding labeling issues.

## 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

In terms of safety, the human safety data provided did not raise any new signals of concern. Based on my review, it is recommended that this NDA be approved.

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

None

#### 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. Pediatric clinical safety, efficacy, and pharmacokinetic studies will be requested for the 2 to 11 years age population as a PMR under PREA.

13.2. Comments to be conveyed to the applicant

None, save for the PREA studies.

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/s/  
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JOEL SCHIFFENBAUER  
12/20/2011