

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022113Orig1s000**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-113  
SERIAL NUMBER: 0019  
DATE RECEIVED BY CENTER: June 21, 2011  
PRODUCT: Advil Allergy & Congestion Relief (Ibuprofen 200 mg, Phenylephrine HCL 10mg, chlorpheniramine maleate 4 mg)  
INTENDED CLINICAL POPULATION: Temporary relief of symptoms associated with hay fever or other upper respiratory allergies and the common cold  
SPONSOR: Pfizer Consumer HealthCare  
DOCUMENTS REVIEWED: 90-day Toxicity Study (b) (4) in the Rat  
REVIEW DIVISION: Division of Nonprescription Clinical Evaluation (HFD-560)  
PHARM/TOX REVIEWER: Wafa Harrouk, Ph.D.  
SECONDARY REVIEWER: Paul Brown, Ph.D.  
DIVISION DIRECTOR: Andrea Leonard-Segal, M.D.  
PROJECT MANAGER: Janice Adams-King, RN, BSN, MS (USPHS)

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## EXECUTIVE SUMMARY

### I. Recommendations

- A. Recommendation on approvability: Recommend approval from the pharmacology/toxicology standpoint.
- B. Recommendation for nonclinical studies: None
- C. Recommendations on labeling: None

### II. Summary of nonclinical findings

**Brief overview of nonclinical findings:** Advil Allergy & Congestion Relief<sup>1</sup> (Ibuprofen 200 mg/Phenylephrine HCl 10mg/ chlorpheniramine maleate 4 mg) is indicated for the temporary relief of symptoms associated with upper respiratory allergies and the common cold. This NDA was initially submitted for review on September 25, 2007 and received a “Not Approvable Letter” (NAL) on July 25, 2008. In this “Complete Response” submitted on June 26, 2011, the sponsor has addressed the deficiencies listed in the 2008 “NAL” which include conducting a 90-day repeat dose toxicity and toxicokinetics study with the degradant (b) (4).

(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, (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 for (b) (4) be conducted in the second review cycle.

(b) (4) has shown no evidence of genotoxicity in the Ames *Salmonella* histidine reversion or the human chromosome aberration assays at concentrations of up to (b) (4) mol/mol and (b) (4) mol/mol relative to the parent compound, phenylephrine, respectively. Similarly, no evidence of toxicity was seen in a 2-week repeat dose toxicity study which was conducted with (b) (4) in the original NDA review cycle when (b) (4) was used at concentrations up to (b) (4) mol/mol or (b) (4) mol/mol relative to phenylephrine, respectively. In this submission, (b) (4) showed no evidence of toxicity in the 90-day repeat dose toxicity study which was conducted at concentrations up to (b) (4) (2 concentrations were used, (b) (4)). Based on the above information, (b) (4) is considered to be qualified at concentrations up to (b) (4) in the proposed IPC formulation.

Toxicokinetics data showed that (b) (4) exposure tended to be higher among treated females (both low and high-dose groups) compared to treated males on both day 1 and day 90

<sup>1</sup> Although the drug formulation is still the same as in the original NDA, the new trade name differs from the one used in the original application, (b) (4).

under the conditions of this study. No drug accumulation was noted on day 90 compared to day 1 of the study. Tmax and t1/2 values were variable, but no sex- or treatment-related differences were apparent. (b) (4) did not appear to cause TK interactions with IBU, PE, or CPH. It should be noted that concentrations of all four analytes in treated plasma were highly variable.

Nonclinical safety issues relevant to clinical use: None

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 22-113

**Review number:** 2

**Sequence number/date/type of submission:** 0019, June 21, 2011, Complete Response to NA letter

**Information to sponsor:** Yes ( ) No (x)

**Sponsor and/or agent:** Pfizer Consumer Health (PHC)

**Reviewer name:** Wafa Harrouk

**Division name:** DNCE

**HFD #:** 560

**Review completion date:** October 24, 2011

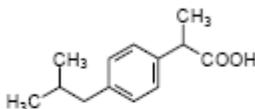
**Drug:**

Trade name: Advil Allergy & Congestion Relief

Generic name: Ibuprofen 200 mg/ Phenylephrine HCL 10mg/chlorpheniramine maleate 2 mg

USAN/INN: Ibuprofen

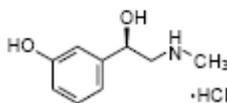
CAS: Benzeneacetic acid,  $\alpha$ -methyl-4-(2-methylpropyl), ( $\pm$ )-



Molecular Formula:  $C_{13}H_{18}O_2$  Molecular Weight: 206.28 CAS: 58560-75-1 ( $\pm$ )

USAN/INN: Phenylephrine hydrochloride

CAS: ( $\alpha R$ )-3-Hydroxy- $\alpha$ -[(methylamino)methyl]benzenemethanol hydrochloride

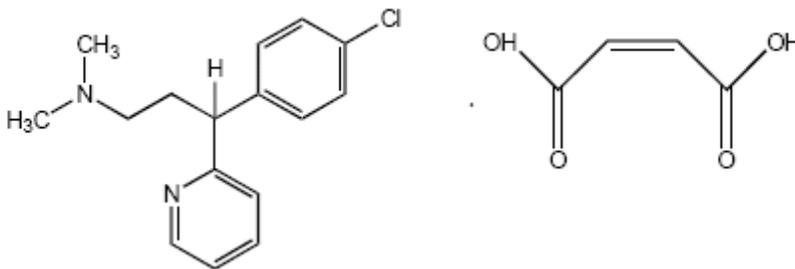


Molecular Formula:  $C_9H_{13}NO_2 \cdot HCl$  Molecular Weight: 203.67 CAS: 61-76-7

Chlorpheniramine:

CAS: 113-92-8

USP Chemical name: 2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-N,N-dimethyl-,  
(Z)-2-butenedioate (1:1), or  
2-[p-Chloro- $\alpha$ -[2-(dimethylamino)ethyl]benzyl]pyridine maleate  
(1:1)  
Molecular Formula: C<sub>16</sub>H<sub>19</sub>ClN<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>  
Molecular Weight: 390.86



**Relevant INDs/NDAs/DMFs:** NDA 22-113 [REDACTED]<sup>(b) (4)</sup>; NDA 21-394 Advil PM Caplets; NDA 20-944 Children's Advil Chewable Tablets; NDA 20-135 Motrin Chew Tabs; NDA 21-441 Advil Allergy Sinus; NDA 20-589 Children's Advil®; NDA 20-402 Advil® Liqui-Gels; NDA 21-373 Children's Advil® Cold; NDA 21-587 Children's Advil® Allergy Sinus.

DMF #'s: [REDACTED]<sup>(b) (4)</sup>

**Drug class:** Non Steroidal Analgesic Drug, alpha adrenergic agonist and antihistamine

**Intended clinical population:** Temporary relief of symptoms associated with hay fever or other upper respiratory allergies and the common cold. One tablet of [REDACTED]<sup>(b) (4)</sup> should be taken every 4 hours while symptoms persist, not to exceed 6 tablets in any 24-hour period. Treatment should last less than [REDACTED]<sup>(b) (4)</sup>, unless directed by a doctor. The drug should be taken by adults and children above 12 years. A doctor consultation is recommended for use in children under 12 years of age. Although the drug duration is recommended for only [REDACTED]<sup>(b) (4)</sup>, allergy tends to last for more than [REDACTED]<sup>(b) (4)</sup>, is recurring and consumers will likely use it repeatedly and for prolonged periods of time which would classify the exposure to this drug as chronic in duration.

**Clinical formulation:**

**Table 1.0-1: Quantitative Composition**

(b) (4)

Ingredient	Compendial Name	mg/caplet	kg/batch	Function
Ibuprofen USP	Ibuprofen	200	561	Active Drug Substance
Phenylephrine HCl USP	Phenylephrine Hydrochloride	10.0	27.1	Active Drug Substance
Chlorpheniramine Maleate USP	Chlorpheniramine Maleate	4.00	10.8	Active Drug Substance
Acesulfame K NF	Acesulfame Potassium	(b) (4)		
Carnauba Wax (b) (4)	Carnauba Wax			
Silicon Dioxide (b) (4) NF	Colloidal Silicon Dioxide			
Starch Corn NF	Corn Starch			
Croscarmellose Sodium NF	Croscarmellose Sodium			
Glyceryl Behenate NF (b) (4)	Glyceryl Behenate			
	Hypromellose			
Microcrystalline Cellulose NF (b) (4)	Microcrystalline Cellulose			
Microcrystalline Cellulose NF (b) (4)	Microcrystalline Cellulose			
Starch Pregelatinized NF - (b) (4)	Pregelatinized Starch			
Propyl Gallate NF (b) (4)	Propyl Gallate			
Silicon Dioxide NF (b) (4)	Silicon Dioxide			
Sucralose (b) (4) NF	Sucralose			

**Route of administration:** Oral caplets

**Disclaimer:** Graphical information is scanned from sponsor’s submission unless stated otherwise.

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of 22-113 are owned by PHC or are data for which PHC has obtained a written right of reference. Any information or data necessary for approval of 22-113 that PHC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that PHC does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-113.

**Studies reviewed within this submission:** A 90-day repeat-dose toxicity and toxicokinetics study in rats.

**Studies not reviewed within this submission:** None

## 2.6.2 PHARMACOLOGY:

The pharmacology profiles of ibuprofen, chlorpheniramine and PE are well established and all 3 ingredients have been approved in several OTC products.

## 2.6.3 PHARMACOLOGY TABULATED SUMMARY

None submitted

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

**Study title:** “A Repeated Dose Ninety-Day Toxicokinetic Study (b) (4) Study # AC09NX.7G31.01.BTL) of IPC (b) (4) in Sprague-Dawley (SD) Rats”

**Study Objective:** The purpose of this study was to assess the toxicokinetic (TK) profiles of the combination test article (Ibuprofen, phenylephrine, chlorpheniramine, IPC) and the degradant (b) (4) following daily oral administration for 90 consecutive days in SD rats.

**Study Design:** IPC (b) (4) was administered orally by gavage to male and female SD rats (4/sex/group) once daily for 90 days. A vehicle-only group received 0.5% methylcellulose, a negative control group received IPC alone (IBU (85.5 mg/kg), PE (4.25 mg/kg) and CPH (1.7 mg/kg). The low dose (IPC-(b) (4)) group consisted of IBU 85.5 mg/kg, PE 4.25 mg/kg, CPH 1.7 mg/kg and (b) (4) 0.3125 mg/kg. The high dose ( (b) (4) ) group consisted of IBU 85.5 mg/kg, PE 4.25 mg/kg, CPH 1.7 mg/kg and (b) (4) 0.625 mg/kg. Blood samples were collected on days 1 and 90 for TK measurements.

Group	Number of animals/time point/sex	Time points	Volume/Tube of Whole Blood*	Days of blood collection
1-2	3	0.5 hours	2 mL (optimal) per animal/ NaF/Na2EDTA	Day 1 and after 90 days of treatment
3-4	3	Predose and 0.25, 0.5, 1.5, 3, 5, and 8 hours post-dose	2 mL (optimal) per animal/ NaF/Na2EDTA	Day 1 and after 90 days of treatment

\*If blood volume collected is less than 2 mL, the approximate blood volume collected was recorded. Plasma from each sample was aliquotted into two vials after harvesting (for the blood collection on Day 1 only).

**Study Results:**

The concentrations of PE and (b) (4) for all formulations met the acceptance criteria of 80-120% of target. No test articles (PE and (b) (4)) were detected in the vehicle control samples. The dose formulations were not analyzed for ibuprofen or chlorpheniramine maleate. Treated rats were exposed to the combination product and to the (b) (4) impurity.

Ibuprofen: There were no gender- or treatment-related differences for IBU exposure TK data. AUCs and Cmax values on Days 1 and 90 were similar between the low and high dose groups. There were no apparent differences in drug exposure between the sexes on Day 1 or 90 in either treatment groups.

Phenylephrine: Differences in Cmax and AUCs between low and high dose groups were only apparent in females on Day 1. There were moderate elevations of Cmax and AUCs particularly in females in both treatment groups at Day 90.

Chlorpheniramine: Moderate difference in Cmax between low and high doses was only apparent in females on Day 1. Mild differences in AUCs between low and high dose groups were observed in both genders at Day 90. There were significant increases in Cmax and AUCs particularly in females in both treatment groups at Day 90.

(b) (4) Plasma exposure increased proportionally with dose and was more apparent in females. Higher Cmax and AUCs were observed in females at day 90.

## 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

In-Text Table 2 Summary of Key IBU Toxicokinetic Parameters

Day	Treatment Group	Sex	AUC <sub>0-last</sub> ng*hr/mL	AUC <sub>0-inf</sub> ng*hr/mL	AUC <sub>0-24</sub> ng*hr/mL	C <sub>max</sub> * ng/mL	T <sub>max</sub> hr	t <sub>1/2</sub> hr	CL/F/kg L/hr/kg	Vss/F/kg L/kg
1	2	Male	NA	NA	NA	37500	NA	NA	NA	NA
		Female	NA	NA	NA	60200	NA	NA	NA	NA
		Overall	NA	NA	NA	48850	NA	NA	NA	NA
1	3	Male	244000	290000	287000	89900	0.50	2.89	0.295	1.23
		Female	311000	386000	381000	86200	0.50	3.14	0.222	1.00
		Overall	277000	338000	334000	88100	0.50	3.03	0.253	1.11
1	4	Male	248000	319000	314000	61200	0.50	3.43	0.268	1.33
		Female	290000	369000	362000	101000	0.50	3.57	0.232	1.19
		Overall	269000	343000	338000	81100	0.50	3.47	0.249	1.25
90	2	Male	NA	NA	NA	86600	NA	NA	NA	NA
		Female	NA	NA	NA	104500	NA	NA	NA	NA
		Overall	NA	NA	NA	95530	NA	NA	NA	NA
90	3	Male	275000	298000	298000	67700	0.25	2.07	0.287	0.857
		Female	328000	374000	372000	154000	0.25	2.53	0.230	0.839
		Overall	302000	335000	334000	111000	0.25	2.30	0.256	0.848
90	4	Male	263000	396000	379000	91600	0.25	4.83	0.226	1.57
		Female	313000	358000	358000	92800	0.25	2.76	0.239	0.952
		Overall	288000	367000	363000	92200	0.25	3.59	0.236	1.22

Source: End-of-Text Table 1.2 and Table 2.2

Note: TK parameters were calculated from mean concentration-time profiles for males, females, and overall using noncompartmental methods. Each mean concentration was derived from 3M, 3F, or 6 total rats for the overall mean profiles; only 1 sample was taken from each animal.

Note: TK parameters except for T<sub>max</sub> are presented with 3 significant figures.

\*Mean concentrations at 0.5 hours are shown for C<sub>max</sub> for Group 2

NA= not applicable since only 0.5 hour plasma sample taken

**In-Text Table 3 Summary of Key PE Toxicokinetic**

Day	Treatment Group	Sex	AUC <sub>0-last</sub> ng*hr/mL	AUC <sub>0-inf</sub> ng*hr/mL	AUC <sub>0-24</sub> ng*hr/mL	C <sub>max</sub> * ng/mL	T <sub>max</sub> hr	t <sub>1/2</sub> hr	CL/F/kg L/hr/kg	Vss/F/kg L/kg
1	2	Male	NA	NA	NA	23.1	NA	NA	NA	NA
		Female	NA	NA	NA	33.7	NA	NA	NA	NA
		Overall	NA	NA	NA	28.4	NA	NA	NA	NA
1	3	Male	130	155	154	55.3	0.25	2.99	22.5	97.2
		Female	117	136	135	24.1	3.0	2.44	25.6	90.4
		Overall	123	147	146	35.3	0.25	2.84	23.8	97.6
1	4	Male	120	140	140	40.3	0.25	2.74	24.8	98.1
		Female	133	182	178	29.7	0.25	3.87	19.2	107
		Overall	127	159	157	35.0	0.25	3.26	21.9	103
1	2	Male	NA	NA	NA	40.2	NA	NA	NA	NA
		Female	NA	NA	NA	56.4	NA	NA	NA	NA
		Overall	NA	NA	NA	48.3	NA	NA	NA	NA
90	3	Male	163	179	179	68.5	0.25	2.07	19.5	59.7
		Female	170	198	196	58.2	0.25	2.61	17.8	65.0
		Overall	167	188	187	63.3	0.25	2.33	18.7	62.5
90	4	Male	146	177	175	45.0	0.25	2.91	19.9	83.6
		Female	159	171	171	58.0	0.50?	1.27	20.1	42.7
		Overall	163	191	189	45.3	0.50?	2.57	18.5	68.0

Source: End-of-Text Table 1.3 and Table 2.3

Note: TK parameters were calculated from mean concentration-time profiles for males, females, and overall using noncompartmental methods. Each mean concentration was derived from 3M, 3F, or 6 total rats for the overall mean profiles; only 1 sample was taken from each animal.

Note: TK parameters except for T<sub>max</sub> are presented with 3 significant figures.

\*Mean concentrations at 0.5 hours are shown for C<sub>max</sub> for Group 2

NA= not applicable since only 0.5 hour plasma sample taken

**In-Text Table 4 Summary of Key CPH Toxicokinetic Parameters**

Day	Treatment Group	Sex	AUC <sub>0-last</sub> ng*hr/mL	AUC <sub>0-inf</sub> ng*hr/mL	AUC <sub>0-24</sub> ng*hr/mL	C <sub>max</sub> * ng/mL	T <sub>max</sub> hr	t <sub>1/2</sub> hr	CL/F/kg L/hr/kg	Vss/F/kg L/kg
1	2	Male	NA	NA	NA	7.65	NA	NA	NA	NA
		Female	NA	NA	NA	13.0	NA	NA	NA	NA
		Overall	NA	NA	NA	10.4	NA	NA	NA	NA
1	3	Male	11.0	13.2	13.2	20.4	0.25	1.52	90.7	198
		Female	11.5	17.1	17.0	6.41	0.50	1.71	70.0	172
		Overall	11.6	15.5	15.5	14.0	0.25	1.64	77.1	182
1	4	Male	7.34	8.24	8.24	12.3	0.25	0.430	145	89.9
		Female	12.8	16.6	16.6	9.19	0.50	1.25	71.9	129
		Overall	11.4	16.0	15.9	10.5	0.25	1.49	74.9	161
90	2	Male	NA	NA	NA	9.64	NA	NA	NA	NA
		Female	NA	NA	NA	23.9	NA	NA	NA	NA
		Overall	NA	NA	NA	16.8	NA	NA	NA	NA
90	3	Male	21.0	22.9	22.9	25.5	0.25	0.851	52.2	64.0
		Female	43.6	47.6	47.6	21.5	0.25	1.38	25.1	50.0
		Overall	34.1	38.9	38.9	23.5	0.25	1.68	31.1	68.0
90	4	Male	22.0	32.5	32.1	14.0	0.25	3.70	37.2	198
		Female	48.3	52.8	52.8	27.5	0.50	1.39	22.8	41.0
		Overall	35.2	40.6	40.5	19.6	0.50	1.77	30.3	62.4

Source: End-of-Text Table 1.1 and Table 2.1

Note: TK parameters were calculated from mean concentration-time profiles for males, females, and overall using noncompartmental methods. Each mean concentration was derived from 3M, 3F, or 6 total rats for the overall mean profiles; only 1 sample was taken from each animal.

Note: TK parameters except for T<sub>max</sub> are presented with 3 significant figures.

\*Mean concentrations at 0.5 hours are shown for C<sub>max</sub> for Group 2

NA= not applicable since only 0.5 hour plasma sample taken

**In-Text Table 5 Summary of Key <sup>(b) (4)</sup> Toxicokinetic Parameters**

Day	Treatment Group	Sex	AUC <sub>0-last</sub> ng*hr/mL	AUC <sub>0-inf</sub> ng*hr/mL	AUC <sub>0-24</sub> ng*hr/mL	C <sub>max</sub> * ng/mL	T <sub>max</sub> hr	t <sub>1/2</sub> hr	CL/F/kg L/hr/kg	Vss/F/kg L/kg
1	3	Male	26.2	NA**	NA**	15.6	0.25	NA**	NA	NA
		Female	53.3	NA**	NA**	19.0	3.0	NA**	NA	NA
		Overall	45.3	NA**	NA**	13.9	3.0	NA**	NA	NA
1	4	Male	41.7	52.9	52.6	15.4	1.5	1.91	11.8	32.6
		Female	114	124	124	27.1	3.0	1.82	5.04	13.2
		Overall	83.7	97.8	97.4	19.1	1.5	2.53	6.39	23.4
90	3	Male	35.0	48.9	49.2	12.5	0.25	2.84	6.36	26.1
		Female	44.1	50.9	51.0?	14.0?	1.5	1.57	6.13	13.9
		Overall	39.5	48.6	48.7	11.0?	0.25	1.96	6.42	18.1
90	4	Male	73.0?	79.3	79.3	14.7	3.0	1.90?	7.89	21.6
		Female	90.9	99.4	99.4	30.6	1.5	1.27	6.29	11.5
		Overall	87.1	93.3	93.2	22.6	1.5	1.83	6.71	17.8

Note: TK parameters were calculated from mean concentration-time profiles for males, females, and overall using noncompartmental methods. Each mean concentration was derived from 3M, 3F, or 6 total rats for the overall mean profiles; only 1 sample was taken from each animal.

Note: TK parameters except for T<sub>max</sub> are presented with 3 significant figures.

\*Mean concentrations at 0.5 hours are shown for C<sub>max</sub> for Group 2

NA= not applicable since only 0.5 hour plasma sample taken

\*\*There was not enough evaluable data in the terminal phase to calculate half-life for <sup>(b) (4)</sup> on Day 1 in Group 3, AUC<sub>0-inf</sub>, AUC<sub>0-24</sub>, CL/F/kg or Vss/F/kg could therefore not be calculated.

## 2.6.6 TOXICOLOGY

**Study title:** “A Repeated Dose Ninety-Day Oral Toxicity (b) (4) Study # AC09NX.7G31.BTL) of IPC (b) (4) in Sprague-Dawley Rats”

**Study Objective:** The purpose of this study was to assess the potential toxicity of the combination test article (Ibuprofen, phenylephrine, chlorpheniramine, IPC) and its impurity (b) (4) following daily oral administration for 90 consecutive days in SD rats.

**Study Design:** IPC- (b) (4) was administered orally by gavage to male and female SD rats (10/sex/group) once daily for 90 days. A vehicle-only group received 0.5% methylcellulose, a negative control group received IPC alone (IBU (85.5 mg/kg), PE (4.25 mg/kg) and CPH (1.7 mg/kg). The low dose (IPC- (b) (4) group consisted of IBU 85.5 mg/kg, PE 4.25 mg/kg, CPH 1.7 mg/kg and (b) (4) 0.3125 mg/kg. The high dose (IPC- (b) (4) group consisted of IBU 85.5 mg/kg, PE 4.25 mg/kg, CPH 1.7 mg/kg and (b) (4) 0.625 mg/kg. Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry and urine parameters, organ weights, and macroscopic and microscopic examinations. Blood samples were collected on days 1 and 90 for TK measurements.

### Study Results:

**Drug stability:** Since stability studies and dose formulation analyses were performed based on the analysis of PE and (b) (4) only and not including ibuprofen and chlorpheniramine maleate, it is not clear whether the bioanalytical and toxicokinetic results of the combination of phenylephrine HCl and (b) (4) with ibuprofen and chlorpheniramine maleate is accurate based on the doses described in the protocol and this report.

**Mortality:** There were 3 preterm deaths in this study.

Case 1: A high-dose treated male was found dead on study day 11. The cause of death was attributed to repeated gavage trauma due to the presence of frothy fluid in the esophagus. Gross pathology examination revealed the presence of fibrin in the connective tissues of the esophagus and hemorrhaging of the lungs.

Case 2: A high-dose treated male was terminated due to moribund status on study day 71. Gross pathology indicated that the cause of death was attributed to the presence of a malignant schwannoma of the brain adjacent to the olfactory bulb in the nasal passage. No other cases of this type of tumors were seen in this study. Malignant schwannomas are considered to be rare tumors in this strain of rats. A literature review conducted by the contract laboratory showed 4 cases of rats with this type of tumor from a similar age group in the SD rat. The report concluded that the rate of schwannomas in the high-dose treatment group is not any greater than has been seen in control treated rats in chronic toxicity studies and thus considered to be an isolated incidence and is not related to the drug treatment. An independent search of the historical controls for the SD rat for (b) (4) showed an incidence rate for the malignant schwannomas to be of 0.28%

as compiled from 30 carcinogenicity studies (b) (4). In the absence of additional data, a cause-effect relationship between the treatment and the presence of the tumor cannot be established.

Case 3: A control-treated female was found dead on study day 52. Gross pathology examination revealed widespread edema in the lungs which is likely to be caused by a gavage error.

**Clinical signs:** No abnormal clinical signs were noted in the vehicle control or IPC control rats during cageside observations. Decreased motor activity was observed once in one low-dose female rat and in one male rat each of the low- and high-dose groups. Due to the low incidence and occurrence on only one day of the study, these signs were not considered to be test article related.

No abnormal clinical signs were noted in the IPC control rats during weekly hands-on observations. Thinness was observed once in one vehicle control male (Day 22), two vehicle control females (Days 71-85), and in one low-dose female (Days 71-85).

**Body weight & mean body weight gains:** There were no compound-related statistically significant differences in weekly mean body weights or mean body weights of either sex when compared to the vehicle control group. There were few random significant changes in weekly body weight gains when compared to the vehicle control group.

**Food consumption:** Statistically significant changes were noted in the IPC control females (Days 43-50) and in the high-dose males (Days 85-91) when compared to the vehicle control. The average daily food consumption throughout the study (Days 1-91) was significantly higher in the IPC control males and high-dose females, when compared to the vehicle control group. However, these findings did not correlate with the decrease in the total body weight gain for the same groups.

**Clinical chemistry:** There were no significant compound-related adverse effects on hematology of either sex under the conditions of this study.

**Organ weights:** There were no significant treatment-related adverse effects on organ weights of either sex under the conditions of this study.

**Gross pathology and Histopathology:** There were no abnormal macroscopic or microscopic observations. Because of the incidence of schwannoma in the high dose treated male, an independent review was requested to review the histopathologic evaluations of sections of brain, eyes, and nasal cavity from all animals in this study; supplemental histologic evaluation of neoplastic tissue in immunostained duplicate sections of brain and nasal cavity from the affected animal and review of clinical signs, macroscopic and microscopic findings in all animals in the same dose group was performed.

(b) (4)

It was also concluded that this neoplasm was considered a spontaneous occurrence since there were no neoplastic or preneoplastic lesions in other organs in the affected animal. In addition, review of brain, eye, and nasal cavity histology sections for all animals evaluated in the study revealed the absence of schwannoma, other neural tumors, or related preneoplastic lesions. The only other findings were lesions of the esophagus related to the inappropriate gavage technique which was the possible cause of death of the other 2 rats as was described in the mortality section above.

**Study Conclusion:** Oral dosing of IPC- (b) (4) and IPC- (b) (4) for 90 days in SD rats caused no significant toxicity. Under the conditions of this study, the following NOAEL (no observed adverse effect level) values were obtained: 85.5 mg/kg ibuprofen, 4.25 mg/kg phenylephrine, 1.7 mg/kg chlorpheniramine and 0.625 mg/kg (b) (4). Margins of safety for (b) (4) were calculated based on the 12- and 36-month stability batches which showed (b) (4) levels of (b) (4) per tablet, respectively. The maximum daily human dose of 6 tablets would provide a total (b) (4) intake of (b) (4), respectively. Based on this information, it was found that the margin of safety for (b) (4) ranges between (b) (4) fold under the conditions of this study.

## 2.6.8 OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:** The sponsor has conducted a 90-day repeated dose toxicity and toxicokinetics study to qualify the degradant (b) (4) as per the qualification guidance (ICH Q3B) for a chronic indication such as the case for this drug which is indicated for allergy symptoms. The study results with (b) (4) do not indicate a toxicity risk to humans to the chronic exposure to this degradant when used in combination with ibuprofen, phenylephrine HCl and chlorpheniramine maleate up to (b) (4) in this 90-day toxicity study. Toxicokinetics data showed adequate exposure to the drug combination and to the (b) (4) impurity following a 90-day exposure period. The (b) (4) degradant is considered qualified at concentration up to (b) (4) in this drug product.

**Unresolved toxicology issues (if any):** None

**Recommendations:** Can be approved from a pharm/tox perspective.

**Suggested labeling:** None

## 2.6.9 APPENDIX/ATTACHMENTS

None

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WAFA HARROUK  
10/28/2011

PAUL C BROWN  
10/28/2011

**PHARMACOLOGY/TOXICOLOGY RESPONSE TO INFORMATION REQUEST**

**NDA number:** 22-113

**Sequence number/date/type of submission:** 0028, January 14, 2010, 90 day oral toxicity questions regarding the TK request

**Information to sponsor:** Yes (x) No ( )

**Sponsor and/or agent:** Wyeth Consumer Health Care (WCHC)

**Manufacturer for drug substance:** WCHC

**Conducting laboratory:** (b) (4)

**Reviewer name:** Wafa Harrouk

**Division name:** DNCE

**HFD #:** 560

**Drug:**

**Trade name:** (b) (4)

**Generic name:** Ibuprofen 200 mg/ Phenylephrine HCL 10mg/chlorpheniramine maleate 2 mg

**Intended clinical population:** Temporary relief of symptoms associated with hay fever or other upper respiratory allergies and the common cold.

**Background:** At the time of the original review cycle, the division recommended that the sponsor conduct a 90-day toxicology study for the qualification of the degradant, (b) (4) if the product were to be approved for use for a period longer than 2 weeks. The sponsor was informed that such a study should use sufficiently high levels of the degradant (b) (4) that can be analytically confirmed. The sponsor was also encouraged to submit a protocol for the qualification study to the Agency for review prior to conducting the study. The sponsor has since provided a protocol for a **90-day Oral Toxicity Study protocol** ((b) (4) Study # AC09NX) for review and comments prior to the initiation of the study (protocol submitted July 31, 2009). Comments on the protocol were communicated to the sponsor (letter dated December 2, 2009), which included a recommendation to collect blood samples for toxicokinetic evaluation (TK).

In a letter dated January 14, 2010, the sponsor responded to the TK request by arguing that WCH believes that TK analysis of the 4 components [Ibuprofen, Chlorpheniramine, Phenylephrine, (b) (4)] in the Advil caplet product is not required for the following reasons:

1. The purpose of the study is to qualify the safety of the (b) (4) degradant. ICH Guidance Q3A and Q3B (R2) Impurities in new drug products (July 2006) do not require TK plasma analysis for qualification of impurities.
2. TK of the active ingredients Ibuprofen, Chlorpheniramine and Phenylephrine are already well characterized in animals and humans. Further TK studies are therefore unnecessary.

3. WCH actively seeks to perform animal studies only when it is absolutely necessary.

Based on the above reasons the sponsor has asked the following questions:

1. Can the Agency clarify its requirement for the need of TK plasma sampling?
2. If the Agency considers that TK plasma analyses on Days 1 and 90 of dosing are still necessary, does the Agency agree that only plasma determinations of (b) (4) will be sufficient?
3. What criteria should be used for evaluation of the data? That is, what TK information would be considered critical for the interpretation of the data from this study?

Discussion:

The toxicokinetic assessment of a drug product is an integral part of the nonclinical testing program. Its value lies in its ability to enhance the value of the toxicological data generated, both in term of predicting plasma concentrations, target tissue doses, and the fate of the administered dose. This information can help in determining the mechanism of toxicity, whenever present, and assist in the interpretation of toxicity data thus improving the risk assessment process. The ICH Guidance Q3A and Q3B (R2) Impurities in new drug products (July 2006) guidance documents only mention briefly the studies required for qualifying impurities, and were not intended to provide a comprehensive list for all the required study design elements for conducting these qualification toxicity studies. General information on the design of toxicology studies can be found in ICH M3 (R2) and ICH S3A on Toxicokinetics.

The following are recommended comments to be conveyed to the sponsor:

1) We are primarily interested in collecting information on the impurity, (b) (4). However, we recommend that you measure the plasma level of the active ingredients (Ibuprofen, Chlorpheniramine, Phenylephrine) in addition to (b) (4). It may be possible to accomplish this by using the same blood samples without having to use additional animals. Such data would confirm adequate exposure to all ingredients in the study and may be helpful in understanding any toxicity observed and in attributing the toxicity to a particular ingredient in the drug product. The findings of such a study in the absence of toxicokinetic data will be difficult to interpret.

3) For guidance on endpoints to be calculated for TK and other aspects of TK design, you can refer to ICH S3A on Toxicokinetics. Calculating endpoints such as AUC, Tmax, Cmax and other endpoints that will be monitored in the clinic for the active ingredients will allow for comparisons to be made between the nonclinical data and the clinical trials.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22113

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ORIG-1

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HEALTHCARE

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 (b) (4)

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WAFI HARROUK  
02/02/2010

PAUL C BROWN  
02/02/2010

**PHARMACOLOGY/TOXICOLOGY MEMO**

**NDA number:** 22-113

**Sequence number/date/type of submission:** 000, July 31, 2009, 90 day oral toxicity protocol in SD rats

**Information to sponsor:** Yes (x) No ( )

**Sponsor and/or agent:** Wyeth Consumer Health Care (CHC)

**Manufacturer for drug substance:** Wyeth CHC

**Conducting laboratory:** (b) (4)

**Reviewer name:** Wafa Harrouk

**Division name:** DNCE

**HFD #:** 560

**Drug:**

**Trade name:** (b) (4)

**Generic name:** Ibuprofen 200 mg/ Phenylephrine HCL 10mg/chlorpheniramine maleate 2 mg

**Intended clinical population:** Temporary relief of symptoms associated with hay fever or other upper respiratory allergies and the common cold.

**Background:** In the original NDA review, (b) (4)

(b) (4) was identified as a degradant in stability samples of the PG-containing formulation and its levels were found to be above the allowed 0.5% impurity relative to phenylephrine based on the ICH Q3B guidance determination. A qualification program consisting of two genotoxicity studies (Ames & human lymphocyte chromosome aberration assays) and one repeat-dose general toxicity study (14-day duration in rats) was performed for (b) (4) thus allowing a 14-day exposure in humans. At the end of the review cycle, the following recommendation was relayed to the sponsor: 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. The sponsor was encouraged to submit a protocol for the qualification study to the Agency for review prior to conducting the study.

**90-day Oral Toxicity Study protocol** ((b) (4) Study # AC09NX): In this submission, the sponsor has provided the protocol for the Division's review and comments prior to the initiation of the study.

**Study design:**

Treatment	Group No.	Number of Animals/sex	
		Males	Females
<u>Vehicle Control</u> 0.5% methylcellulose (medium viscosity) in water	1	10	10
<u>Test Article Control</u> IPC alone	2	10	10
<u>Low dose</u> IPC- (b)(4) (mol/mol)	3	10	10
<u>High dose</u> IPC- (b)(4) (mol/mol)	4	10	10
Total		40	40

The following drug concentrations will be used:

Test Article Control: IPC alone  
IBU 85.5 mg/kg  
PE 4.25 mg/kg  
CPH 1.7 mg/kg

Low Dose: IPC- (b)(4) (mol/mol)  
IBU 85.5 mg/kg  
PE 4.25 mg/kg  
CPH 1.7 mg/kg

High Dose: IPC (b)(4) (mol/mol)  
IBU 85.5 mg/kg  
PE 4.25 mg/kg  
CPH 1.7 mg/kg

**Observations:**

Procedure	Main Study Animals
Body Weight**	Weekly starting on SD 1 and terminal weight on SD 91
Food Consumption	Weekly starting on SD 1
Morbidity and Mortality check	Twice Daily at least 6 hours apart
Cage Side Observations	Daily within 2 hours after the last dose administration
Detailed Hands-on Clinical Observations	SD 1 and weekly thereafter (procedure will be performed at the time animals are weighed)

\*Body weights will also be measured on the date of unscheduled sacrifice of Main Study animals.

Clinical pathology (hematology, clinical chemistry) will be evaluated at the end of the study, ophthalmology (pretest & on day 89 or 90 prior to the end of the study), necropsy including organ weights & histopathology will be evaluated. No Toxicokinetic evaluation was proposed.

**Conclusions:**

The general outline of the protocol seems acceptable. Please indicate whether blood samples will be collected from treated rats for toxicokinetic evaluation.

You need to comment on the stability conditions of the test article solution that will be administered to the treatment groups. At this point, the following clarifications are sought out:

1. Clearly state the acceptability criteria that will be used to determine the stability of solutions
2. Confirm that dosing solutions are stored in similar amber glass containers as stability samples.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22113

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HEALTHCARE

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 (b) (4)

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WAFI HARROUK  
11/17/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-113  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: July 09, 2007  
PRODUCT: (b) (4) caplets (Ibuprofen 200 mg/  
Phenylephrine HCL 10mg/chlorpheniramine maleate  
4 mg)  
INTENDED CLINICAL POPULATION: Temporary relief of symptoms associated with hay  
fever or other upper respiratory allergies and the  
common cold  
SPONSOR: Wyeth Consumer HealthCare  
DOCUMENTS REVIEWED: Multiple submissions in the electronic document  
room (SN0000-0009)  
REVIEW DIVISION: Division of Nonprescription Clinical Evaluation  
(HFD-560)  
PHARM/TOX REVIEWER: Wafa Harrouk, Ph.D.  
PHARM/TOX TEAM LEADER: Paul Brown, Ph.D.  
DIVISION DIRECTOR: Andrea Leonard-Segal, M.D.  
PROJECT MANAGER: Elaine Abraham R.Ph.

Date of review submission to Division File System (DFS): July 9, 2008

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## EXECUTIVE SUMMARY

### I. Recommendations

- A. Recommendation on approvability: Recommend approvable from the pharmacology/toxicology standpoint for short term use up to 2 weeks.
- B. Recommendation for nonclinical studies: To support approval for longer duration of use (>2 weeks), a longer duration (90 day) toxicity study should be conducted to adequately qualify the (b)(4) degradant identified in the stability testing.
- C. Recommendations on labeling: None

### II. Summary of nonclinical findings

**Brief overview of nonclinical findings:** (b)(4) (Ibuprofen 200 mg/Phenylephrine HCl 10mg/ chlorpheniramine maleate 4 mg) is indicated for the temporary relief of symptoms associated with upper respiratory allergies and the common cold. In this NDA, The sponsor has used phenylephrine HCl (PE; 10 mg) as the nasal decongestant ingredient to provide an alternative to the pseudoephedrine HCl (30 mg) product currently available on the market. Pseudoephedrine (PSE)-containing products have recently been moved behind the counter as per the "Combat Methamphetamine Epidemic Act of 2005" legislation which restricted sales of PSE Over-The-Counter (OTC). The proposed formulation is intended to eliminate the behind the counter restriction on this cough and cold medicine to allow for easy OTC access with clear new labeling which indicates the presence of the PE instead of the PSE ingredient.

In the pre-NDA meeting with the sponsor held on March 19, 2007, the sponsor had proposed a formulation which produced among other degradants an (b)(4) degradant of phenylephrine referred to as (b)(4). During the degradation qualification program, the sponsor identified a positive mutagenicity signal for the Ames Assay and decided to reformulate the product. The sponsor tested the use of an antioxidant preservative, propyl gallate (PG), a GRAS ingredient listed under "substances added directly to human food" as per 21 CFR 184.1660 (b)(4) PG acts as an (b)(4).

A final panel report on the safety assessment of PG in cosmetics was included in this submission. Dermal animal toxicity studies showed no adverse effect when PG was used at concentrations up to 5% in rats, mice, dogs and guinea pigs. The panel recommended that PG is safe to use in cosmetics at concentrations not to exceed 1%. Carcinogenicity studies were conducted by the National Toxicology Program (NTP) using oral feeding studies in mice and rats; both studies concluded that PG does not have

<sup>1</sup> Journal of American College of Toxicology, Volume 4, # 3 1985

the ability to induce tumors under the conditions of the conducted studies. The addition of PG (b) (4)

(b) (4) was identified as a degradant in stability samples of the PG-containing formulation and its levels were found to be above the allowed 0.5% impurity relative to phenylephrine based on the ICH Q3B guidance determination. (b) (4) underwent a qualification program consisting of two genotoxicity studies and one repeat-dose general toxicity study:

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

(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) mol/mol and (b) (4) mol/mol relative to phenylephrine, respectively. Similarly, no evidence of toxicity was seen in the general toxicity studies in rats at concentrations of up to (b) (4) mol/mol or (b) (4) mol/mol relative to phenylephrine, respectively. Therefore, (b) (4) is considered qualified at concentrations up to (b) (4)

Pharmacologic activity: Decongestant

Nonclinical safety issues relevant to clinical use: None

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 22-113

**Review number:** 1

**Sequence number/date/type of submission:** 000, July 9, 2007, New NDA application

**Information to sponsor:** Yes ( ) No (x)

**Sponsor and/or agent:** Wyeth CHC

**Manufacturer for drug substance:** Wyeth Consumer Health Care

**Reviewer name:** Wafa Harrouk

**Division name:** DNCE

**HFD #:** 560

**Review completion date:** July 8, 2008

**Drug:**

**Trade name:** (b) (4)

**Generic name:** Ibuprofen 200 mg/ Phenylephrine HCL 10mg/chlorpheniramine maleate 2 mg

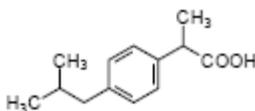
**Chemical name:**

**CAS registry number:**

**Molecular formula/molecular weight & Structure:**

**USAN/INN:** Ibuprofen

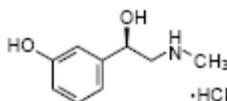
**CAS:** Benzeneacetic acid,  $\alpha$ -methyl-4-(2-methylpropyl), ( $\pm$ )-



**Molecular Formula:** C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>    **Molecular Weight:** 206.28    **CAS:** 58560-75-1 ( $\pm$ )

**USAN/INN:** Phenylephrine hydrochloride

**CAS:** ( $\alpha$ R)-3-Hydroxy- $\alpha$ -[(methylamino)methyl]benzenemethanol hydrochloride



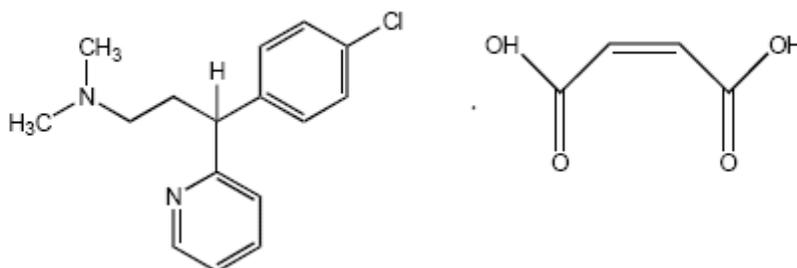
**Molecular Formula:** C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub> · HCl    **Molecular Weight:** 203.67    **CAS:** 61-76-7

Chlorpheniramine:

CAS: 113-92-8

USP Chemical name: 2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-N,N-dimethyl-,  
(Z)-2-butenedioate (1:1), or  
2-[p-Chloro- $\alpha$ -[2-(dimethylamino)ethyl]benzyl]pyridine maleate  
(1:1)Molecular Formula: C<sub>16</sub>H<sub>19</sub>ClN<sub>2</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

Molecular Weight: 390.86



**Relevant INDs/NDAs/DMFs:** The sponsor is proposing to use phenylephrine HCl (10 mg) as the nasal decongestant ingredient to provide an alternative to the pseudoephedrine HCl (30 mg) product currently marketed under the (b) (4) (NDA #21-441).

**Drug class:** Decongestant

**Intended clinical population:** Temporary relief of symptoms associated with hay fever or other upper respiratory allergies and the common cold. One tablet of (b) (4) should be taken every 4 hours while symptoms persist, not to exceed 6 tablets in any 24-hour period. Medication should last less than (b) (4), unless directed by a doctor. The drug should be taken by adults and children above 12 years. A doctor consultation is recommended for use in children under 12 years of age. Although the drug duration is recommended for only (b) (4), allergy tends to last for more than (b) (4), is recurring and consumers will more likely use it for prolonged periods of time which would accumulate to a life time exposure of more than 6 months which would classify the exposure to this drug as chronic.

**Clinical formulation:** In addition to the active ingredients (Ibuprofen 200 mg/ Phenylephrine HCL 10mg/chlorpheniramine maleate 4 mg), the proposed formulation contains the following excipients:

Table 1.0-1: Excipients in (b) (4)

Excipient	Reference to Standards
<b>Compendial – Non-novel</b>	
Acesulfame Potassium	NF
Carnauba Wax	NF
Colloidal Silicon Dioxide	NF
Corn Starch	NF
Croscarmellose Sodium	NF
Glyceryl Behenate	NF
Hypromellose	USP
(b) (4)	USP
Microcrystalline Cellulose (b) (4)	NF
Microcrystalline Cellulose (b) (4)	NF
Pregelatinized Starch	NF
Propyl Gallate	NF
Silicon Dioxide	NF
Sucralose	NF
(b) (4)	

**Table 1.0-1: Quantitative Composition** (b) (4)

Ingredient	Compendial Name	mg/caplet	kg/batch	Function
Ibuprofen USP	Ibuprofen	200	561	Active Drug Substance
Phenylephrine HCl USP	Phenylephrine Hydrochloride	10.0	27.1	Active Drug Substance
Chlorpheniramine Maleate USP	Chlorpheniramine Maleate	4.00	10.8	Active Drug Substance
Acesulfame K NF	Acesulfame Potassium	(b) (4)		
Carnauba Wax (b) (4)	Carnauba Wax			
Silicon Dioxide (b) (4) NF	Colloidal Silicon Dioxide			
Starch Corn NF	Corn Starch			
Croscarmellose Sodium NF	Croscarmellose Sodium			
Glyceryl Behenate NF (b) (4)	Glyceryl Behenate			
	Hypromellose			
Microcrystalline Cellulose NF (b) (4)	Microcrystalline Cellulose			
Microcrystalline Cellulose NF (b) (4)	Microcrystalline Cellulose			
Starch Pregelatinized NF - (b) (4)	Pregelatinized Starch			
Propyl Gallate NF (b) (4)	Propyl Gallate			
Silicon Dioxide NF (b) (4)	Silicon Dioxide			
Sucralose NF (b) (4)	Sucralose			

(Cont'd)

(b) (4)



**Route of administration:** Oral caplets

**Disclaimer:** Graphical information is scanned from sponsor's submission unless stated otherwise.

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of 22-113 are owned by Wyeth or are data for which Wyeth has obtained a written right of reference. Any information or data necessary for approval of 22-113 that Wyeth does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Wyeth does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-113.

**Toxicology Evaluation:** The only toxicology issue relevant to this application resided in the amount of degradants that were detected during the stability testing of the product.

According to the CMC reviewer, all Ibuprofen-Related Impurities and Degradants results were less than the applicable reporting limits at all time points and storage conditions tested.

All Phenylephrine Hydrochloride-Related Impurities and Degradant results were less than the applicable specifications at all time points and storage conditions tested except for three new Phenylephrine degradants which were identified during the stability study:

(b) (4)

All Chlorpheniramine Maleate (CPM)-Related Impurities and Degradants results were less than the applicable reporting limit at all time points and storage conditions tested with the exception of (b) (4) of CPM. In the 12-month 25°C/60%RH samples, this degradant was (b) (4) relative to CPM; among the 6-month 40°C/75%RH samples, it ranged from (b) (4). Based on the ICH Threshold for Identification and extensive history of safe use of Chlorpheniramine Maleate in OTC products (GRASE status per 21CFR341), a limit of NMT (b) (4) was previously proposed for unspecified CPM related degradants for the post-approval stability program. Based on these data and a safety assessment of the degradant, a limit of NMT (b) (4) is proposed for CPM (b) (4) the post-approval stability program.

**Studies reviewed within this submission:** (b) (4) a degradant of Phenylephrine and maleic acid underwent a qualification program which consisted of two genotoxicity studies and one repeat-dose general toxicity study.

- Ames *Salmonella* histidine reversion assay

- Human lymphocyte chromosome aberration assay
- 2-week general toxicity study in rats spiked with (b) (4).

**Studies not reviewed within this submission:**

- The following study (14-day (b) (4) toxicity study) was not reviewed since the sponsor changed the final formulation to include PG (b) (4) such that a degradant qualification program would not be required. However, it is worth mentioning that the 14-day oral gavage studies for the (b) (4) degradant would not be accepted as qualification studies due to the inconsistency in the level of degradant administered during the study period for the (b) (4) study. (b) (4) did not have a potential for mutagenicity when tested in the Ames test ((b) (4) was found positive in a high-dose group in one study but results were not reproducible in a repeat study), human chromosomal aberration assay or the in vivo micronucleus assay in rats. The overall genotoxic testing battery for the degradant product, (b) (4), is considered negative for potential mutagenicity and clastogenicity.
- Validation of an Analytical Method for the (b) (4)

## 2.6.2 PHARMACOLOGY:

Pharmacology of ibuprofen, chlorpheniramine and PE are well established and all 3 ingredients have been approved in several OTC products.

## 2.6.3 PHARMACOLOGY TABULATED SUMMARY

None submitted

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

None submitted

## 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None submitted

## 2.6.6 TOXICOLOGY

**Impurities and degradant qualification:** Due to their presence at levels which do not exceed those permitted as per the ICH impurities (Q3B) guidance under the conditions tested, there was no need to qualify any of the impurities/degradants listed in the tables below except for (b) (4).

(b) (4)

**1. Study title: “Bacterial Reverse Mutation Assay” (Ames assay; Study #:**  
**(b) (4) AC09NX.503.BTL)**

**Study Objective:** The purpose of this study was to evaluate the mutagenic potential of IPC-(b) (4) (ibuprofen phenylephrine-chlorpheniramine-(b) (4)) by measuring its ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* tester strains, and at the tryptophan locus of an *Escherichia coli* tester strain in the presence and absence of S9 activation. The test article component ratios were as follows: ibuprofen at 93%, phenylephrine hydrochloride at 4.6%, chlorpheniramine maleate at 1.8% and (b) (4) mol/mol relative to phenylephrine).

**Study Design:** DMSO was the vehicle control and 2-nitrofluorene, sodium azide, 9-aminoacridine, methyl methanesulfonate and 2-aminoanthracene were used as positive controls.

Tester strains were *Salmonella* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 *uvrA*. All dose levels of IPC-<sup>(b) (4)</sup>, vehicle control and positive controls were plated in duplicate for the initial toxicity-mutation assay and in triplicate for the confirmatory mutagenicity assay. In the initial toxicity-mutation assay, IPC-<sup>(b) (4)</sup> was tested with all tester strains in the presence and absence of Aroclor-induced rat liver S9 metabolic activation at 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate. In the confirmatory mutagenicity assay, IPC-<sup>(b) (4)</sup> was tested with all tester strains in the presence and absence of Aroclor-induced rat liver S9 metabolic activation at 50, 150, 500, 1500 and 5000 µg per plate. The initial toxicity-mutation assay and the confirmatory mutagenicity assay were conducted using the plate incorporation method.

**Study Results:** In the initial toxicity-mutation assay, neither precipitate nor toxicity was observed. No positive mutagenic response was observed. In the confirmatory mutagenicity assay, neither precipitate nor background lawn toxicity was observed. The vehicle control and positive controls fulfilled the requirements for a valid assay. In conclusion, IPC-<sup>(b) (4)</sup> was not mutagenic in this bacterial reverse mutation assay with *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 *uvrA* in either the presence or absence of Aroclor-induced rat liver S9 metabolic activation.

### 7.21 Summary of the Initial Toxicity-Mutation Assay

Test Article Id : IPC-<sup>(b)</sup><sub>(4)</sub>(ibuprofen-phenylephrine-chloropheniramine-<sup>(b)</sup><sub>(4)</sub>)  
 Study Number : AC09NX.503.BTL  
 Experiment No : B1

Average Revertants Per Plate ± Standard Deviation										
Activation Condition	None									
Dose (µg/plate)	TA98		TA100		TA1535		TA1537		WP2 <i>uvrA</i>	
Vehicle	22	± 3	124	± 1	22	± 6	12	± 1	23	± 1
1.5	11	± 4	138	± 8	27	± 3	7	± 1	20	± 4
5.0	21	± 2	136	± 1	25	± 5	9	± 1	14	± 2
15	17	± 8	178	± 4	21	± 4	7	± 3	13	± 2
50	16	± 1	156	± 1	20	± 4	6	± 3	16	± 4
150	19	± 8	157	± 1	24	± 4	7	± 0	18	± 3
500	20	± 1	158	± 3	25	± 3	10	± 4	16	± 4
1500	15	± 6	150	± 8	28	± 2	9	± 1	19	± 1
5000	12	± 1	152	± 5	23	± 2	9	± 5	16	± 0
Positive	135	± 8	493	± 29	418	± 42	1113	± 86	115	± 4

Activation Condition	Rat Liver S9									
Dose (µg/plate)	TA98		TA100		TA1535		TA1537		WP2 <i>uvrA</i>	
Vehicle	23	± 6	174	± 2	14	± 2	9	± 2	20	± 0
1.5	19	± 5	164	± 8	20	± 6	9	± 5	22	± 4
5.0	23	± 1	172	± 15	15	± 10	10	± 1	23	± 4
15	30	± 3	163	± 4	16	± 0	13	± 6	26	± 1
50	25	± 1	179	± 13	15	± 2	13	± 4	20	± 2
150	17	± 7	180	± 21	16	± 1	9	± 1	18	± 0
500	24	± 5	201	± 13	22	± 7	11	± 1	24	± 7
1500	21	± 1	181	± 11	15	± 5	9	± 1	23	± 3
5000	20	± 0	193	± 23	11	± 1	8	± 1	21	± 5
Positive	593	± 20	610	± 25	149	± 6	74	± 28	252	± 48

Vehicle = Vehicle Control

Positive = Positive Control (50 µL plating aliquot)

Plating aliquot = 50 µL

### 7.22 Summary of the Confirmatory Mutagenicity Assay

Test Article Id : IPC<sup>(b)(4)</sup> (ibuprofen-phenylephrine-chlorpheniramine<sup>(b)(4)</sup>)  
 Study Number : AC09NX.503.BTL  
 Experiment No : B2

Average Revertants Per Plate ± Standard Deviation

Activation Condition	None									
Dose (µg/plate)	TA98		TA100		TA1535		TA1537		WP2 <i>uvrA</i>	
Vehicle	13	± 5	147	± 24	11	± 2	6	± 5	14	± 1
50	11	± 3	152	± 19	14	± 6	7	± 4	15	± 3
150	13	± 3	146	± 23	15	± 4	6	± 4	11	± 4
500	14	± 7	159	± 10	14	± 3	7	± 2	11	± 2
1500	12	± 4	169	± 11	13	± 2	6	± 2	12	± 2
5000	10	± 7	149	± 10	12	± 4	2	± 1	13	± 6
Positive	170	± 42	647	± 42	284	± 59	740	± 276	117	± 15

Activation Condition	Rat Liver S9									
Dose (µg/plate)	TA98		TA100		TA1535		TA1537		WP2 <i>uvrA</i>	
Vehicle	19	± 5	189	± 8	11	± 3	9	± 2	17	± 1
50	17	± 3	184	± 14	8	± 7	5	± 3	13	± 5
150	20	± 3	163	± 9	14	± 5	8	± 2	21	± 2
500	20	± 3	150	± 27	15	± 3	4	± 1	14	± 3
1500	16	± 4	142	± 11	13	± 1	4	± 2	14	± 6
5000	10	± 1	154	± 30	9	± 4	4	± 1	20	± 3
Positive	520	± 66	607	± 20	106	± 15	80	± 34	297	± 36

Vehicle = Vehicle Control

Positive = Positive Control (50 µL plating aliquot)

Plating aliquot = 50 µL

Historical Negative and Positive Control Values 2004 – 2006									
revertants per plate									
Strain	Control	Activation							
		None				Rat Liver			
		Mean	SD	Min	Max	Mean	SD	Min	Max
TA98	Neg	18	6	5	56	27	8	6	72
	Pos	184	129	30	1812	666	434	61	2669
TA100	Neg	132	31	52	632	141	29	67	267
	Pos	545	147	112	4349	828	410	168	2652
TA1535	Neg	20	7	4	49	16	5	4	45
	Pos	376	131	44	998	114	60	24	985
TA1537	Neg	7	3	1	20	8	3	1	22
	Pos	692	343	14	2216	101	97	13	1297
WP2 <i>uvrA</i>	Neg	18	7	5	53	19	7	4	59
	Pos	151	98	28	892	394	268	29	1296

SD=standard deviation; Min=minimum value; Max=maximum value; Neg=negative control (including but not limited to deionized water, dimethyl sulfoxide, ethanol and acetone); Pos=positive control

**Study Conclusion:** IPC <sup>(b) (4)</sup> (ibuprofen phenylephrine chlorpheniramine-<sup>(b) (4)</sup>) was not mutagenic in the Ames Assay under the conditions of this study.

**2. Study Title: “*In vitro* mammalian chromosome aberration test”** <sup>(b) (4)</sup>  
**Study #: AC09NX.341.BTL)**

**Study Objective:** The purpose of this study was to evaluate the clastogenic potential of IPC <sup>(b) (4)</sup> (ibuprofen at 93%, phenylephrine hydrochloride at 4.6%, chlorpheniramine maleate at 1.8% and <sup>(b) (4)</sup> mol/mol relative to phenylephrine), based on its ability to induce chromosome aberrations in human peripheral blood lymphocytes (HPBL).

**Study Design:** The study consisted of a preliminary toxicity assay and a chromosome aberration assay. The clastogenic potential of the IPC-<sup>(b) (4)</sup> was evaluated by measuring the frequency of cells with structural chromosome aberrations in HPBL cultures treated with the test article in comparison with the frequency in cultures treated with the solvent only. The test article was also assessed for its potential to induce numerical chromosome aberrations. DMSO was used as a vehicle control and either Mitomycin C (in the absence of S9) or Cyclophosphamide (in the presence of S9) was used as positive controls.

The dose levels selected for microscopic evaluation of chromosome aberrations were 0 (solvent control), 100, 250 and 500 $\mu$ g/mL, and one positive control concentration for the non-activated 4-hour exposure group, 0 (solvent control), 50, 100 and 250 $\mu$ g/mL, and one positive control concentration for the S9-activated 4-hour exposure group, and 0 (solvent control), 50, 150 and 350 $\mu$ g/mL, and one positive control concentration for the non-activated 20-hour exposure group. Substantial toxicity, indicated by a 50% or greater reduction in the mitotic index relative to the corresponding solvent control, was achieved at the highest dose level selected for evaluation of chromosome aberrations for each exposure group. For each of the exposure groups, there was no increase in the percentage of cells with structural or numerical chromosome aberrations compared with the corresponding solvent control at any of the test article concentrations evaluated microscopically. The solvent and positive controls fulfilled the requirements for a valid test.

**Table 4-1: Dosages Selected for Chromosome Aberration Assay**

<b>Treatment Condition</b>	<b>Treatment Time</b>	<b>Recovery Time</b>	<b>Dosages (<math>\mu</math>g/mL)</b>
Non-activated	4 hr	16 hr	25, 50, 100, 150, 250, 350, 500
	20 hr	0 hr	25, 50, 100, 150, 250, 350, 500
S9-activated	4 hr	16 hr	50, 100, 250, 500, 750, 1000, 1200

**Study Results:** IPC-<sup>(b) (4)</sup> did not induce structural chromosome aberrations or numerical chromosome aberrations in the non-activated test system and in the S9-activated test system in the in vitro mammalian chromosome aberration test using human peripheral blood lymphocytes.

## 7.7 Summary

Treatment µg/mL	S9 Activation	Treatment Time	Mean Mitotic Index	Cells Scored		Aberrations per Cell (Mean +/- SD)		Cells with Aberrations	
				Numerical	Structural	(Mean +/- SD)	(%)	Numerical (%)	Structural (%)
DMSO	-S9	4	7.4	200	200	0.000	±0.000	0.0	0.0
IPC- <sup>(b)</sup> (4)									
100	-S9	4	6.4	200	200	0.000	±0.000	0.0	0.0
250	-S9	4	6.8	200	200	0.000	±0.000	0.0	0.0
500	-S9	4	3.4	200	200	0.000	±0.000	0.0	0.0
MMC, 0.6	-S9	4	4.1	200	100	0.200	±0.492	0.0	16.0**
DMSO	+S9	4	6.9	200	200	0.000	±0.000	0.0	0.0
IPC- <sup>(b)</sup> (4)									
50	+S9	4	6.9	200	200	0.000	±0.000	0.0	0.0
100	+S9	4	4.7	200	200	0.000	±0.000	0.0	0.0
250	+S9	4	3.3	200	200	0.000	±0.000	0.0	0.0
CP, 20	+S9	4	5.0	200	100	0.200	±0.426	0.0	19.0**
DMSO	-S9	20	6.9	200	200	0.000	±0.000	0.0	0.0
IPC- <sup>(b)</sup> (4)									
50	-S9	20	6.4	200	200	0.000	±0.000	0.0	0.0
150	-S9	20	6.0	200	200	0.000	±0.000	0.0	0.0
350	-S9	20	2.8	200	200	0.000	±0.000	0.0	0.0
MMC, 0.3	-S9	20	5.0	200	100	0.220	±0.543	0.0	17.0**

**Treatment:** Cells from all treatment conditions were harvested at 20 hours after the initiation of the treatments.

**Aberrations per Cell:** Severely damaged cells were counted as 10 aberrations.

**Percent Aberrant Cells:** \* p≤0.05; \*\* p≤0.01; using the Fisher's exact test.

HISTORICAL CONTROL VALUES  
STRUCTURAL CHROMOSOME ABERRATIONS  
2005-2007

NON-ACTIVATED TEST SYSTEM

Historical Values	Percent Aberrant Cells (%)	
	Solvent Control <sup>1</sup>	Positive Control <sup>2</sup>
Mean	0.0	17.6
Standard Deviation	±0.1	±4.4
Range	0.0-0.5	5.5-40.0

S9 ACTIVATED TEST SYSTEM

Historical Values	Percent Aberrant Cells (%)	
	Solvent Control <sup>1</sup>	Positive Control <sup>3</sup>
Mean	0.0	17.0
Standard Deviation	±0.1	±3.1
Range	0.0-0.5	9.0-24.0

<sup>1</sup> Solvents include water, saline, DMSO, ethanol, acetone, and other non-standard and Sponsor-supplied vehicles.

<sup>2</sup> Positive control for non-activated studies is mitomycin C (MMC).

<sup>3</sup> Positive control for S9 activated studies is cyclophosphamide (CP).

**Study Conclusion:** Under the conditions of the assay described in this report, IPC- (b) (4) was concluded to be negative for the induction of structural chromosome aberrations and numerical chromosome aberrations in the non-activated test system and in the S9-activated test system in the in vitro mammalian chromosome aberration test using human peripheral blood lymphocytes.

**3. Study title: “A Repeated Dose Two Week Oral Toxicity Study In Sprague-Dawley Rats” ( (b) (4) Study # AC09NX.2G31.BTL)**

**Study Objective:** The purpose of this study was to assess the potential toxicity of the test article containing the (b) (4) degradant following daily oral administration for 14 consecutive days.

**Study Design:** IPC- (b) (4) was administered orally by gavage to male and female Sprague-Dawley rats (5/sex/group) once daily for 14 days. The control group received IPC alone (IBU (85.5 mg/kg), PE (4.25 mg/kg) and CPH (1.7 mg/kg)). The low dose (IPC- (b) (4) group consisted of IBU 85.5 mg/kg, PE 4.25 mg/kg, CPH 1.7 mg/kg and (b) (4). The high dose (IPC- (b) (4) group consisted of IBU 85.5 mg/kg, PE 4.25 mg/kg,

CPH 1.7 mg/kg and (b) (4). Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry and urine parameters, organ weights, and macroscopic and microscopic examinations.

**Study Results:**

**Drug stability:** New formulations were prepared every six days for the two week study. The vials were stored at 2 to 8°C awaiting delivery for dosing.

For (b) (4) and PE content, IPC alone was found to be stable for at least 36 hours at room temperature and for at least 7 days at 2-8 °C.

For (b) (4) content, the (b) (4) IPC-(b) (4) (mol/mol) formulation was found to be stable for at least 36 hours at 2-8 °C. At 5 and 7 days, the (b) (4) IPC-(b) (4) formulation failed the acceptance criteria for stability at 2-8°C. For 36 hours at room temperature, the (b) (4) IPC (b) (4) formulation failed the acceptance criteria for stability.

For PE content, the (b) (4) IPC-(b) (4) (mol/mol) formulation was found to be stable for at least 36 hours at room temperature and for at least 7 days at 2-8°C.

For PE and (b) (4) content, (b) (4) IPC (b) (4) (mol/mol) formulation was found to be stable for at least 36 hours at room temperature and for at least 7 days at 2-8 °C.

The sponsor states that all formulations analyzed met the acceptance criteria for homogeneity and accuracy, and were used within the established stability period. However, from the stability data above for the (b) (4) IPC (b) (4), the formulation seems to have failed the acceptance criteria for stability at 2-8°C on days 5 & 7.



**Mortality:** There were no compound-related effects on mortality. There were 3 deaths in the study. The sponsor believes that the cause of death was due to gavage accidents for all 3 cases:

- The first was an IPC-treated male which was found dead on study day 5 with discharge noted around the mouth prior to its death.

- The second animal (group 3, male) was found dead on study day 15 during urine collection. The animal showed ruffled fur and a discharge from the nose and mouth, gasping and decreased motor activity were noted prior to death.
- The third animal (group 3, female) was found dead on Day 13 and the death was considered to be due to a gavage accident based on microscopic examination. Discharge from the nose was noted on Day 13 prior to death.

**Clinical signs:** No treatment-related clinical signs were noted.

**Table 3.3-1: Summary of Incidence of Clinical Observations (Cageside)**

Treatment (Group No.)	Control (Group 1) IPC alone	Low Dose (Group 2) IPC- (b) (4) mol/mol	High Dose (Group 3) IPC- (b) (4) mol/mol
No. Animals /Sex	5	5	5
<b>Males</b>			
Thin Appearance	1	NA	NA
Decreased Motor Activity	1	NA	NA
Ruffled Fur	1	NA	NA
Hunched Appearance	1	NA	NA
Gasping	1	NA	NA
Discharge (Nose)	1	1	NA
Discharge (Mouth)	1	NA	NA
<b>Females</b>			
Thin Appearance	NA	1	NA
Ruffle Fur	NA	1	NA
Stained Coat (Mouth)	NA	1	NA
Hunched Back	NA	1	NA
Gasping	NA	2	NA

NA. Not applicable

**Body weight, mean body weight gains and total food consumption:** There were no compound-related adverse effects on mean body weight, mean body weight gain or food consumption of either sex.

**Mean hematology:** There were no compound-related adverse effects on hematology of either sex.

**Clinical chemistry:** In males, creatinine kinase (CPK) in groups 2 and 3 and Total Protein (TP) and Globulin in Group 3 was statistically significantly decreased when compared to Group 1. Chloride levels were significantly decreased in Group 3-treated females compared to controls. However, all changes fell within the accepted reference range for the laboratory historical control data.

**Organ weights:** Relative heart and lung weights were significantly increased in the Group 2 females when compared to control-treated animals. There were no statistically significant findings in the males when compared to Group 1. However, no dose-response was noted for the group 3 females or for treated males compared to controls. In addition, no correlation between the heart weight and histopathology data was noted.

**Gross pathology and Histopathology:** There were no abnormal macroscopic or microscopic observations. The only findings were lesions of the esophagus related to the inappropriate gavage technique.

**Study Conclusion:** Oral dosing of IPC- (b) (4) and IPC- (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 IPC- (b) (4) in Sprague Dawley rats. The stability data for the IPC- (b) (4) 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.

## 2.6.8 OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:** 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.

**Unresolved toxicology issues (if any):** 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. The sponsor is encouraged to submit a protocol for the qualification study for the Agency to review prior to conducting the study.

Recommendations: Approvable for use up to 2 weeks.

Suggested labeling: None

## 2.6.9 APPENDIX/ATTACHMENTS

None submitted

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/s/

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Wafa Harrouk  
7/9/2008 03:24:40 PM  
PHARMACOLOGIST

Paul Brown  
7/11/2008 12:03:55 PM  
PHARMACOLOGIST

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 22-113

**Applicant:** Wyeth Consumer Healthcare    **Stamp Date:** September 25, 2007

**Drug Name:** (b) (4)

**NDA Type:** 505(b)(2)

On **initial** overview of the NDA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	x		
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	N/A		
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?	N/A		
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A  
NEW NDA/BLA**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	N/A		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	N/A		
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	x		A 14-day general toxicity study, an Ames Salmonella study & a study for chromosome aberration in human lymphocyte were submitted to qualify the <span style="background-color: gray; color: gray;">(b) (4)</span> <span style="background-color: gray; color: gray;">2</span> degradants formed during product formulation
11	Has the sponsor addressed any abuse potential issues in the submission?	N/A		
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	x		
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

Any Additional Comments:

Wafa Harrouk

November 14, 2007

\_\_\_\_\_  
Reviewing Pharmacologist

\_\_\_\_\_  
Date

David Jacobson-Kram

November 14, 2007

\_\_\_\_\_  
Team Leader/Supervisor

\_\_\_\_\_  
Date

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A  
NEW NDA/BLA**

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/s/

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Wafa Harrouk  
11/16/2007 10:49:21 AM  
PHARMACOLOGIST

David Jacobson-Kram  
12/5/2007 11:42:51 AM  
PHARMACOLOGIST

## 2.6 PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

**NDA:** 505(b) application for [REDACTED] (b) (4)  
[REDACTED] for [REDACTED] (b) (4)  
(Ibuprofen 200 mg/Phenylephrine 10 mg/Chlorpheniramine  
4 mg): NDA # 22-113.

**Information to sponsor:** Yes (x) No ( )

**Sponsor and/or agent:** Wyeth Consumer HealthCare (CHC)

**Reviewer name:** Wafa A. Harrouk, Ph.D.

**Division name:** Division of Non-Prescription Clinical Evaluation, Office of Non-Prescription Products (ONP)

**HFD #:** 560

**Review completion date:** March 14, 2007

**Proposed clinical study:** None

## BACKGROUND

Wyeth CHC is proposing to submit two 505(b)(2) applications for [REDACTED] (b) (4)  
[REDACTED] (Ibuprofen 200 mg/Phenylephrine 10  
mg/Chlorpheniramine 4 mg): NDA # 22-113, to replace Ibuprofen 200  
mg/pseudoephedrine HCL 30 mg tablets and Ibuprofen 200 mg/pseudoephedrine HCl 30  
mg/Chlorpheniramine maleate 2 mg, respectively to comply with the legislation on “The  
combat Methamphetamine Epidemic Act of 2005”.

It is of note that the sponsor is proposing to increase the level of chlorpheniramine  
maleate from 2 mg to 4 mg, to correspond with the monograph dose for adults and  
children over the age of 12 years of age (CFR 341).

## NONCLINICAL ISSUES

### Issue 1: Propyl gallate

In an earlier meeting with the division dated May 10, 2005, the sponsor had  
proposed 2 formulation which contained [REDACTED] (b) (4)  
[REDACTED] degradant ([REDACTED] (b) (4)), which has been  
qualified and met the ICH guideline for not requiring additional toxicology studies. More  
recently, the sponsor has used [REDACTED] (b) (4), propyl gallate, [REDACTED] (b) (4)  
[REDACTED] Propyl gallate is listed  
as GRAS under “substances added directly to human” as per 21 CFR 184.1660 [REDACTED] (b) (4)  
[REDACTED] (b) (4). A final panel report on the safety assessment of propyl gallate in

cosmetics was included<sup>1</sup> in this submission. Dermal animal toxicity studies showed no effect when PG was used at concentrations up to 5% in rats, mice, dogs and guinea pigs. The panel recommended that PG is safe to use in cosmetics at concentrations not to exceed 1%. Carcinogenicity studies were conducted by NTP using oral feeding studies in mice and rats; both studies concluded that PG does not have the ability to induce tumors under the conditions of the studies. The proposed formulation containing propyl gallate and a comparison to the previous formulation is shown below.



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<sup>1</sup> Journal of American College of Toxicology, Volume 4, # 3 1985

NDA 22-113:

## II. FORMULATION SIMILARITY – NDA 22-113

(b) (4)

The non-PG formulation and the PG formulation compositions listed in Table 1 are identical, except for the addition of an antioxidant preservative, propyl gallate.

Table 1. Formulation Comparison

Ingredient	Non-PG (mg / caplet)	PG (mg / caplet)	Function
Ibuprofen USP	200	200	Active Drug Substance
Phenylephrine HCl USP	10.0	10.0	Active Drug Substance
Chlorpheniramine Maleate USP	4.00	4.00	Active Drug Substance
Acesulfame K NF			(b) (4)
Carnauba Wax (b) (4)			
Silicon Dioxide Colloidal NF (b) (4)			
Sarch Corn NF			
Croscarmellose Sodium NF			
Glyceryl Behenate NF (b) (4)			
(b) (4)			
Microcrystalline Cellulose (b) (4)			
Microcrystalline Cellulose			
Starch Pregelatinized NF - 1551			
Silicon Dioxide NF (b) (4)			
Sucralose (U) (S) NF			
(b) (4)			
Propyl Gallate, EP/BP			

\* does not appear in the final dosage form, essentially removed during processing

According to the sponsor proposed formulation, human exposure to PG would be (b) (4) and 7.14 mg/day for NDA 22-113 (assuming a maximum daily dose of 6 caplets each of which contains 1.03 mg and 1.19 mg, respectively).

Issue 2: Genotoxicity findings:

The Sponsor included an attachment summarizing the genotoxicity findings (b) (4) where 3 assays, the Ames test, human lymphocyte chromosome aberration and in vivo rat micronucleus assay, were conducted. The Ames test was found to be positive at the highest dose used but no positive signal was seen in the other 2 assays. No study reports were included. The sponsor goes on to present an argument on why the positive data point in the Ames assay should not pose a safety signal for the proposed NDAs based on: 1) the latest guidance document: "Recommended approaches to integration of Genetic Toxicology Study results"; 2) a discussion of approved drugs which had a positive signal in the Ames assay which carry no warning label and 3) recent expert opinion concerning interpretation of genotoxicity tests.

The sponsor did not have any nonclinical questions.

List of sponsor's questions:

1. Does the Agency agree that the proposed stability data package will be acceptable for filing the NDA, i.e., 3 months accelerated data on PG formulations plus 6 months accelerated data on non-PG formulations?

2. *Does the Agency agree that the proposed stability data package provided during Agency review, will be acceptable to support 18-month expiry dating on the PG formulations, i.e., 6 months accelerated data on the PG formulations and 12 real time data for all formulations?*
3. *Does the Agency agree that a request for a waiver of bioequivalence studies demonstrating equivalence between the formulas will be acceptable for NDA filing, assuming:*
- a) *Dissolution data are adequate to satisfy the requirement for in vitro testing under this waiver request, and*
  - b) *Results of the in vivo bioavailability/bioequivalence studies on the non-PG formulations are found to be acceptable?*
4. *Does the Agency concur that the agreements reached on the three previous questions apply equally to both applications: [REDACTED]<sup>(b) (4)</sup> NDA 22-1 13 (see Attachment II for Data for NDA 22-113)*

## **OVERALL CONCLUSIONS AND RECOMMENDATIONS**

- 1) There are no pharm/tox concerns regarding the use of propyl gallate in the proposed formulations for [REDACTED]<sup>(b) (4)</sup> NDA 22-113.
- 2) No pharm/tox comments regarding the positive genotoxicity signal can be made before the final study reports for the battery of genotoxicity studies are submitted for review and evaluation.

### **Comment to sponsor:**

Final study reports for all genotoxicity assays conducted as discussed in your toxicology overview (attachment 1) will need to be submitted for the Division's review and evaluation at the time of the NDA submission.

Comments were emailed to the sponsor prior to the meeting. Sponsor responded by agreeing to the Division's request.

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this page is the manifestation of the electronic signature.**  
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/s/

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4/4/2007 11:41:32 AM  
PHARMACOLOGIST/TOXICOLOGIST

Kenneth Hastings  
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PHARMACOLOGIST