CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-565

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-565
Submission Date	7/28/09
Brand Name	Advil Cold & Sinus PE
Generic Name	Ibuprofen/Phenylephrine
Reviewer	Ying Fan, Ph.D.
Team Leader (Acting)	Partha Roy, Ph.D.
Primary Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
Medical Division	Office of Non-Prescription Products/Division of Non-Prescription Clinical Evaluation (ONP/DNCE)
Sponsor	Wyeth Consumer Healthcare (WCH)
Submission Type	Original
Dosage Form; Strength	Caplets; 200 mg Ibuprofen/10 mg Phenylephrine
Proposed Indication	Temporary relief of the following symptoms associated with the common cold or flu: headache, fever, sinus pressure, nasal congestion, minor aches and pains.
Proposed Dosage Regimen	Take 1 caplet every 4 hours while symptoms persist, do not use more than 6 caplets in any 24 hour period unless directed by a doctor

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

The sponsor (Wyeth Consumer Healthcare) is submitting a 505 (b)(2) new drug application (NDA) for a new combination of ibuprofen (IBU) (200 mg) and phenylephrine (PE or PHE) (10 mg). The purpose is to provide an alternative to the ibuprofen (200 mg)/pseudoephedrine HCl (30 mg) product currently marketed under the trade name Advil Cold & Sinus (NDA 19-771) with the indication of temporary relief of symptoms associated with the common cold or flu for ages 12 and above.

The original application for this new combination was submitted on July 9, 2007 and the sponsor received a Not Approvable (NA) letter for NDA 22-112 on May 7, 2008. The deficiencies cited in the NA letter from the Clinical Pharmacology perspective were: 1) the submitted PK data for phenylephrine was unreliable due to major flaws in the analytical assay methodology; 2) a cross-study comparison of ibuprofen PK data from the pivotal Study AQ-05-03 to the historical ibuprofen PK data revealed that the mean Tmax values of ibuprofen increased approximately 0.6 hr when combined with phenylephrine, 3) additionally, a lower ibuprofen Cmax value was observed under fed conditions compared to fasted conditions. The sponsor was asked to submit pharmacokinetic data for unconjugated (free) phenylephrine using an adequately validated analytical assay method. The sponsor was also asked to address the potential impact of delayed T_{max} in the presence of phenylephrine, and lower C_{max} under fed conditions on clinical efficacy.

In the current submission (NDA 22-565), the sponsor conducted three new pharmacokinetic (PK) studies to address the deficiencies communicated to them in the NA letter.

No clinical efficacy and safety trial was conducted. A total of three human pharmacokinetic studies, Study AQ-08-12, Study AQ-08-13 and Study AQ-06-08, have been submitted in support of this NDA. Study AQ-08-12 is a three-way crossover, formulation effect/drug interaction bioavailability study with the final to-be-marketed formulation of ibuprofen/phenylephrine. Study AQ-09-13 is a six-way cross over, food effect/drug interaction bioavailability study with the final to-be-marketed formulation of ibuprofen/phenylephrine. Study AQ-06-08 is a study designed as a bridge between the IBU/PE formulation studied in AQ-05-03 and the formulation intended for commercialization. Study AQ-05-03 was previously reviewed in the original NDA review cycle (refer to Dr. Lei Zhang's Clinical Pharmacology review for NDA 22-112 dated April 28, 2008), however no data from AQ-05-03 have been used in this review cycle.

A site inspection was conducted by the Division of Scientific Investigations (DSI) for the clinical and analytical portions of the pivotal PK studies, Study AQ-08-12 and Study AQ-08-13.

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed the Clinical Pharmacology information for NDA 22-565 submitted on July 28, 2009 and finds it acceptable, pending satisfactory DSI inspection.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

This application is mainly supported by two pharmacokinetic studies (Study AQ-08-12 and Study AQ-08-13). Study AQ-08-12 evaluated the bioequivalence of the test product with IBU 200 mg and PE 10 mg single entity products administered concomitantly, and IBU 200 mg single entity product administered alone. Study AQ-08-13 evaluated the bioequivalence of the test product with IBU 200 mg single entity product administered alone, and PE 10 mg single entity product administered alone. In addition, food effect was also assessed in Study AQ-08-13.

The data from Study AQ-08-12 suggested no formulation effect (Tables 1 and 2, Treatment A vs. Treatment B). Ninety percent (90%) confidence intervals (CIs) around the point estimates for AUCL, AUCI and Cmax of IBU met the BE 80-125% criteria. Compared to single ingredient ibuprofen (Advil), phenylephrine appeared to delay Tmax of ibuprofen by 0.5 hr (Table 1, Treatment A vs. Treatment C), consistent with the data previously submitted in the original submission.

Table 1. Mean (SD) IBU Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-12).

	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=41)	72.7 (21.2)	74.0 (21.7)	19. 6 (4.1)	2.0 (0.3-6.0)
B (n=41)	72.5 (19.6)	73.7 (19.9)	21.3 (5.8)	2.0 (0.5-4.0)
C (n=41)	75.7 (21.9)	77.0 (22.3)	22.2 (5.3)	1.5 (0.5-6.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/B*	99.7 (96.4-103.0)	99.6 (96.4-103.0)	93.8 (87.5-100.5)	—
A/C*	95.9 (92.8-99.2)	96.0 (92.8-99.2)	89.5 (83.5-95.9)	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: Motrin IB Tablet + Sudafed PE Tablet - Fasted
C: Advil-Fasted

Table 2: Mean (SD) Free PE Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-12)

	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=41)	1018.8 (295.8)	1058.4 (303.5)	1139.7 (640.6)	0.5 (0.2-2.0)
B (n=41)	980.1 (249.9)	1016.1 (254.7)	1139.2 (580.1)	0.3 (0.2-2.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/B*	103.5 (97.2-110.3)	103.7 (97.5-110.4)	100.0 (87.3-114.6)	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: Motrin IB Tablet + Sudafed PE Tablet - Fasted

Study AQ-08-13 evaluated food effect and drug-drug interaction. Under fasted conditions, the test product met the BE 80-125% criteria for geometric mean ratios when compared to Motrin IB and Sudafed PE in terms of AUC and Cmax (Table 3). Tmax of IBU in the combination caplet was achieved 28 minutes later than for Motrin IB. The data from Study AQ-08-13 suggested that under fed conditions, the test product met the BE criteria (90% CI between 80-125) for IBU compared to Motrin IB for both AUC and Cmax, and only for AUC and not for Cmax for free PE when compared to Sudafed PE (Tables 3 and 4). The lower bound of the 90% confidence interval for free PE Cmax was outside the lower limit for BE, 76.4% (Table 4). For IBU, the 90% CIs for AUCL and AUCI for the comparison of IBU+PE caplet under fed conditions vs. fasted conditions (B/A ratio) were within 80-125%; the 90% CI for Cmax (fed/fasted) was 79.8-96.1%, very close to the lower bound limit (Table 3). The mean Cmax of IBU (19.5 µg/mL) was comparable under fed and fasting conditions [< 10% lower under fed conditions than mean

Cmax (21.2 μg/mL) under fasting conditions]. Median T_{max} value was 0.6 hr longer under fasted compared to the fed condition. For phenylepherine, the 90% CIs for AUCL and AUCI for the comparison of IBU+PE caplet under fed condition vs. fasted condition (B/A ratio) was within 80-125%; however, the geometric mean ratio and 90% CI for Cmax (fed/fasted) was 77.8 (66.3-91.3%) (Table 4). The mean Cmax of free PE (695.1 μg/mL) was about 15.5% lower under fed condition than mean Cmax (822.0 μg/mL) under fasted condition. Median T_{max} value was shorter under fasted compared to the fed condition.

These findings on delayed T_{max} of IBU in the presence of PE and lower free PE C_{max} values under fed condition were brought to the attention of the Clinical team.

Table 3. Mean (SD) IBU Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-13)

	AUCL (mcg•h/mL)	**AUCI (mcg•h/mL)**	**C_{max} (mcg/mL)**	**T_{max}** (hr)**
Mean (SD)				
A (n=42)	76.1 (15.7)	77.2 (15.7)	21.2 (5.6)	2.0 (0.5-6.0)
B (n=42)	63.3 (11.2)	65.9 (11.5)	19.5 (7.3)	1.4 (0.5-4.0)
C (n=42)	75.7 (14.5)	76.7 (14.5)	23.3 (5.6)	1.6 (0.5-4.0)
D (n=42)	62.3 (10.4)	63.7 (10.5)	20.3 (8.1)	1.1 (0.3-4.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/C*	100.4 (97.8-103.2)	100.6 (98.0-103.2)	91.2 (83.1-103.2)	—
B/D*	101.3 (98.7-104.1)	103.2 (100.5-105.9)	96.0 (87.5-105.2)	—
B/A*	83.5 (81.3-85.8)	85.8 (83.6-88.0)	87.6 (79.8-96.1)	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: IBU + PHE Caplet – Fed
C: Motrin IB Tablet – Fasted
D: Motrin IB Tablet – Fed

Table 4. Mean (SD) Free PE Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-13)

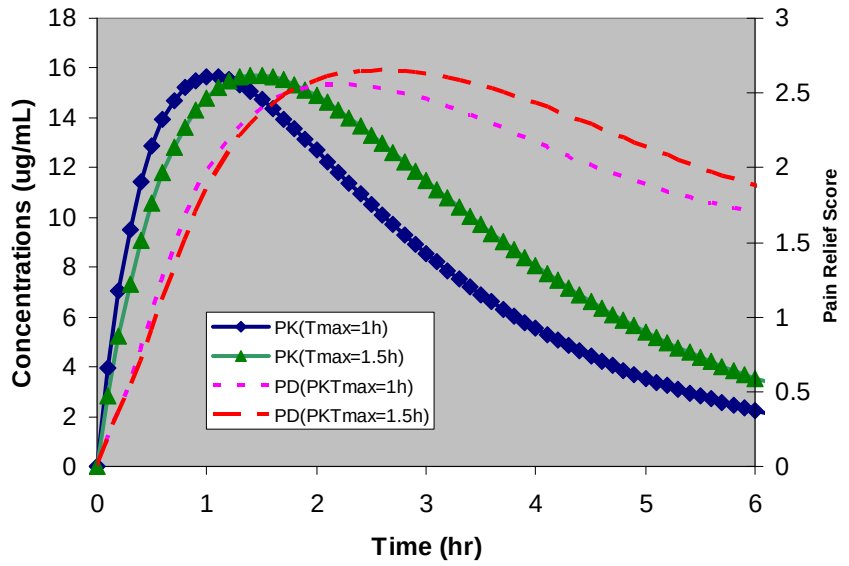
	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=42)	754.2 (188.0)	790.1 (193.7)	822.0 (336.8)	0.5 (0.2-0.8)
B (n=42)	824.8 (211.9)	854.6 (218.5)	695.1 (352.3)	0.8 (0.3-3.0)
E (n=42)	716.0 (196.3)	753.3 (200.1)	867.7 (560.8)	0.3 (0.2-1.0)
F (n=42)	828.9 (216.6)	864.8 (235.3)	819.4 (522.9)	0.7 (0.3-4.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/E*	106.7 (102.4-111.2)	106.2 (101.9-110.8)	100.9 (86.0-118.4)	__
B/F*	99.6 (95.5-103.8)	99.1 (95.1-103.3)	89.7 (76.4-105.3)	__
B/A*	108.2 (103.9-112.8)	107.0 (102.6-111.5)	77.8 (66.3-91.3)	__

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: IBU + PHE Caplet – Fed
E: Sudafed PE Tablet – Fasted
F: Sudafed PE Tablet – Fed

Because no clinical trial was conducted with this new combination product of IBU and PE, ibuprofen PK/PD model for analgesic (dental pain) was used to help understand the likely impact of delayed T_{max} of IBU in combination with PE on clinical efficacy.

The pharmacometics reviewer (Dr. Atul Bhattaram) conducted simulations using the estimated PK-PD with Berkeley Madonna® to evaluate the impact of delay in Tmax on pain relief. Figure 1 shows the time course of plasma concentrations of ibuprofen from two formulations with Tmax of 1 h and 1.5 h. The difference in Tmax reflects the reported differences in Tmax of ibuprofen by 0.5 h between IBU/PE and other formulations. The differences in Tmax do not appear to translate into major differences in pain relief score. Also the observed Tmax of ibuprofen from the proposed IBU/PE formulation is in similar range to other approved IBU formulations. (See the Appendix 4.2 for the review by the Pharmacometrics Team).

Figure 1. Mean time course of plasma ibuprofen concentrations and pain relief from two formulations with Tmax of 1h and 1.5h.



An optional inter-division level clinical pharmacology briefing was held on January 4, 2010.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is the regulatory history of Advil Cold & Sinus PE caplet?

The sponsor first submitted the 505 (b)(2) new drug application (NDA) on July 9, 2007 for a new combination of ibuprofen (IBU) (200 mg) and phenylephrine (PE) (10 mg) under NDA 22-112 to provide an alternative to the ibuprofen (200 mg)/pseudoephedrine HCl (30 mg) product currently marketed under the trade name Advil Cold & Sinus (NDA 19-771) with the indication of temporary relief of symptoms associated with the common cold or flu for ages 12 and above.

The combination of the over-the-counter (OTC) analgesic ibuprofen (IBU) with the nasal decongestant pseudoephedrine hydrochloride (PSE) was approved as a solid dosage form in 1989 (NDA19-771), as a suspension in 2002 (NDA 21-373) and as a liquid-filled capsule in 2002 (NDA 21-374). The solid oral dosage form product is being reformulated with the substitution of phenylephrine hydrochloride (PE) for PSE. This reformulation is to decrease the availability of PSE-containing products and thus decrease the opportunity for illicit conversion of PSE to methamphetamine.

The sponsor intends to offer Advil Cold & Sinus PE (IBU/PE) as an over-the-counter (OTC) alternative to the pseudoephedrine product Advil Cold and Sinus (NDA 19-771), which was moved behind-the-counter in compliance with legislation restricting the sale of all pseudoephedrine-containing drug products (The Combat Methamphetamine Epidemic Act of 2005).

The sponsor received a Not Approvable (NA) letter for NDA 22-112 on May 7, 2008. The deficiencies cited in the NA letter from the Clinical Pharmacology perspective were: 1) the submitted PK data for phenylephrine was unreliable due to major flaws in the analytical assay methodology; 2) a cross-study comparison of ibuprofen PK data from the pivotal Study AQ-05-03 to the historical ibuprofen PK data revealed that the mean Tmax values of ibuprofen increased approximately 0.6 hr when combined with phenylephrine, 3) additionally, a lower ibuprofen Cmax value was observed under fed conditions compared to fasted conditions. The sponsor was asked to submit pharmacokinetic data for unconjugated (free) phenylephrine using an adequately validated analytical assay method. The sponsor was also asked to address the potential impact of delayed T_{max} in the presence of phenylephrine, and lower C_{max} under fed conditions on clinical efficacy.

In response to that, in current submission (NDA 22-565), the sponsor conducted three new pharmacokinetic (PK) studies to address the deficiencies communicated to them in the NA letter.

2.2 General Clinical Pharmacology

2.2.1 What clinical studies were conducted to support this NDA?

This is a 505 (b)(2) application. No clinical efficacy and safety trial was conducted. A total of 2 pivotal human pharmacokinetic studies (study AQ-08-12 and study AQ-08-13) and 1 supportive pharmacokinetic study (study AQ-05-03) have been submitted in support of this NDA. Study AQ-08-12 is a three-way crossover, formulation effect and drug interaction bioavailability study and Study AQ-08-13 is a six-way crossover, food effect and drug interaction, relative bioavailability study of the to-be-marketed formulation ibuprofen 200 mg/phenylephrine 10 mg. Study AQ-06-08 is a study designed as a bridge between the IBU/PE formulation studied in AQ-05-03 and the formulation intended for commercialization. Study AQ-05-03 was previously reviewed in the original NDA review cycle (refer to Dr. Lei Zhang's Clinical Pharmacology review for NDA 22-112 dated April 28, 2008), however no data from AQ-05-03 have been used in this review cycle.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response?

The gender effect on ibuprofen and free phenylephrine PK was analyzed.

For ibuprofen, females have higher AUC and Cmax values (Table 2.3.1.1). In test product (IBU/PE), ibuprofen showed 27.1-38.9% higher exposure than male subjects (Table 2.3.1.2). When individual body weight was taken into considerations, the differences decreased and female showed only 2.5-12.3% higher exposure than males indicating that body weight is the main reason for the difference (Table 2.3.1.2)

Table 2.3.1.1 Within-Gender Comparisons - IBU Pharmacokinetic Parameters (Mean, SD, and 90% CI, Study AQ-08-13)

Treatment	AUCL (mcg•h/mL)		C_{max} (mcg/mL)	
Mean (SD)				
	Males (N=21)	Females (N=21)	Males (N=21)	Females (N=21)
A#	67.0 (11.4)	85.6 (14.0)	17.8 (4.3)	24.8 (4.5)
B	59.3 (8.1)	67.3 (12.6)	18.1 (6.3)	20.9 (8.1)
C	68.1 (10.0)	83.4 (14.4)	20.1 (4.1)	26.5 (5.0)
D	58.8 (8.6)	65.7 (11.0)	18.7 (6.5)	21.9 (9.3)
Ratio (90% CI) ^				
A/C* %	98.3 (94.5-102.2)	102.8 (99.0-106.8)	88.2 (78.9-98.7)	94.9 (81.4-110.6)
B/D* %	100.7 (96.8-104.7)	101.9 (98.2-105.7)	96.1 (85.9-107.5)	95.7 (82.4-111.2)
B/A* %	88.8 (85.4-92.3)	78.5 (75.6-81.5)	98.0 (87.6-109.6)	77.7 (66.7-90.5)

* Reference product
^Based on fitted log-transformed parameters.
A: IBU+PE Caplet – fasted; B: IBU+PE Caplet – Fed; C: Motrin IB Tablet – fasted; D: Motrin IB Tablet –fed
Subject No. 212 (female subject) withdrew voluntarily before period 6. The treatment assigned for this period was A. Consequently, the summary statistics, ratio, and 90% CI for all PK parameters for the female group in treatment A were based on 20 subjects.

Table 2.3.1.2 Ibuprofen Exposure Comparison in Test Product (IBU/PE) Based on Gender.

	Male (N=21)	Female (N=21)	% Difference (Female vs. Male)	Weight adjusted Male *	Weight adjusted Female*	% Difference with Weight adjusted (Female vs. Male)
Cmax (µg/mL)	17.8	24.8	+ 38.9	1363.6	1530.8	+ 12.3
AUCL (µg*h/mL)	67.0	85.6	+ 27.7	5161.5	5317.4	+ 3.0
AUCI (µg*h/mL)	68.2	86.6	+ 27.1	5250.7	5383.3	+ 2.5

+: females>males

*: The units for weight adjusted Cmax, AUCL, AUCI are µg*kg/mL, µg*h*kg/mL, and µg*h*kg/mL, respectively.

For phenylephrine, females have slightly higher AUC and Cmax values when the body weight is not taken into consideration (Table 2.3.1.3). In test product (IBU/PE), free phenylephrine in female subjects showed 1.1% to 18.2% higher exposure than that in male subjects (difference is 1.1% for Cmax; 17.0% and 18.2% for AUCL and AUCI, respectively, Table 2.3.1.4). When body weight was taken into considerations, the differences decreased and female showed -18% to -2.6 % lower exposure than males indicating that body weight is one of the reasons for the differences observed (Table 2.3.1.4)

Table 2.3.1.3 Within Gender Comparison-free PE pharmacokinetic parameters (Mean, SD, and 90% CI, Study AQ-08-12)

Treat-ment	AUCL (pg•h/mL)		C_{max} (pg/mL)	
Mean (SD)				
	Males (N=21)	**Females (N=20)**	**Males (N=21)**	**Females (N=20)**
A	940.9 (225.5)	1100.7 (341.9)	1133.5 (715.3)	1146.3 (570.3)
B	889.7 (248.7)	1074.9 (218.7)	1120.3 (709.1)	1158.9 (422.5)
Ratio (90% CI) ^				
A/B* %	106.5 (96.4-117.5)	101.3 (92.5-110.9)	104.2 (83.0-130.8)	97.2 (82.2-114.9)

* Reference product

^Based on fitted log-transformed parameters.

A: IBU+PE Caplet –fasted;

B: Single Entities (Motrin IB Tablet plus Sudafed PE Tablet administered concomitantly) – fasted

Table 2.3.1.4 Free PE Exposure Comparison Based on Gender

	Male (N=21)	Female (N=20)	% Difference (Female vs. Male)	Weight adjusted Male *	Weight adjusted Female*	% Difference with Weight adjusted (Female vs. Male)
Cmax (µg/mL)	1133.5	1146.3	1.1	87912.3	71731.9	-18
AUCL (µg*h/mL)	940.9	1100.7	17.0	72515.1	69902.5	-3.6
AUCI (µg*h/mL)	972.2	1148.9	18.2	74949.9	73009.5	-2.6

+: females>males; -: females<males

*: The units for weight adjusted Cmax, AUCL, AUCI are µg*kg/mL, µg*h*kg/mL, and µg*h*kg/mL, respectively.

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

2.5.1 Is there a formulation effect for the combination product?

No. The data suggested no formulation effect on IBU and PE PK as assessed by relative bioavailability of the new combination caplet to Motrin IB and Sudafed PE administered together (Treatment A vs. Treatment B) (Tables 2.5.1.1 and 2.5.1.2). For IBU, 90% CIs for the ratios of AUCL, AUCI and Cmax met the BE 80-125% criteria (Table 2.5.1.1). For PE, 90% CIs for the ratios of AUCL, AUCI and Cmax also met the BE criteria (Table 2.5.1.2).

Table 2.5.1.1 Mean (SD) IBU Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-12)

	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=41)	72.7 (21.2)	74.0 (21.7)	19. 6 (4.1)	2.0 (0.3-6.0)
B (n=41)	72.5 (19.6)	73.7 (19.9)	21.3 (5.8)	2.0 (0.5-4.0)
C (n=41)	75.7 (21.9)	77.0 (22.3)	22.2 (5.3)	1.5 (0.5-6.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/B*	99.7 (96.4-103.0)	99.6 (96.4-103.0)	93.8 (87.5-100.5)	—
A /C*	95.9 (92.8-99.2)	96.0 (92.8-99.2)	89.5 (83.5-95.9)	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: Motrin IB Tablet + Sudafed PE Tablet - Fasted
C: Advil-Fasted

Table 2.5.1.2 Mean (SD) Free PE Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-12)

	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=41)	1018.8 (295.8)	1058.4 (303.5)	1139.7 (640.6)	0.5 (0.2-2.0)
B (n=41)	980.1 (249.9)	1016.1 (254.7)	1139.2 (580.1)	0.3 (0.2-2.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/B*	103.5 (97.2-110.3)	103.7 (97.5-110.4)	100.0 (87.3-114.6)	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: Motrin IB Tablet + Sudafed PE Tablet - Fasted

2.5.2 Is there any drug-drug interaction between IBU and PE?

No. The effect of PE on IBU PK and the effect of IBU on PE PK were assessed in Study AQ-08-13 and Study AQ-08-12.

The mean AUCI and Cmax of IBU+PE caplet (fasted) were equivalent to the AUCI and Cmax from the IBU Motrin and Advil data (Table 2.5.2.1, Table 2.5.2.2). Also, the mean AUCI and Cmax of IBU+PE caplet (fasted) were equivalent to the AUCI and Cmax from the PE Sudafed data (Table 2.5.2.3). In the absence of formulation effect concluded in section 2.5.1, these data suggest lack of any drug-drug interaction in terms of systemic exposure between the two active

drug components. The Tmax, however, from the IBU Motrin was shorter than the combination caplet when administered under fasted conditions (99.8 min vs. 131.4 min, Figure 2.5.2.1 and Figure 2.5.2.2) suggesting that the presence of PE delays the rate of absorption of IBU.

Table 2.5.2.1 IBU PK results (n=42, Study AQ-08-13)

Treatment	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max}** (min)	$T_{1/2}$ (h)**
Mean (SD)					
A	76.1 (15.7)	77.2 (15.7)	21.2 (5.6)	2.0 (0.5-6.0)	1.9 (1.4-2.5)
C	75.7 (14.5)	76.7 (14.5)	23.3 (5.6)	1.6 (0.5-4.0)	1.9 (1.6-2.7)
Geometric Mean Ratio (%) (90% Confidence Intervals)^					
A/C*%	100.4 (97.8-103.2)	100.6 (98.0-103.2)	91.2 (83.1-103.2)	—	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
C: Motrin IB Tablet – Fasted

Table 2.5.2.2 IBU PK results (n=41, Study AQ-08-12)

Treatment	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max}** (hr)	$T_{1/2}$ (h)**
Mean (SD)					
A	72.7 (21.2)	74.0 (21.7)	19. 6 (4.71)	2.0 (0.3-6.0)	1.9 (1.3-3.0)
C	75.7 (21.9)	77.0 (22.3)	22.2 (5.3)	1.5 (0.5-6.0)	2.0 (1.3-2.8)
Geometric Mean Ratio (%) (90% Confidence Intervals)^					
A/C*%	106.7 (102.4-111.2)	106.2 (101.9-110.8)	100.9 (86.0-118.4)	—	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
C: Advil-Fasted

Table 2.5.2.3 Free PE PK results (n=42, Study AQ-08-13)

Treatment	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max}** (min)	$T_{1/2}$ (h)**
Mean (SD)					
A	754.2 (188.0)	790.1 (193.7)	822.0 (336.8)	26.2 (18.9-33.5)	1.4 (0.6-5.4)
E	716.0 (196.3)	753.3 (200.1)	867.7 (560.8)	26.5 (14.6-38.4)	1.5 (0.6-5.9)
Geometric Mean Ratio (%) (90% Confidence Intervals)^					
A/E*%	106.7 (102.4-111.2)	106.2 (101.9-110.8)	100.9 (86.0-118.4)	—	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
E: Sudafed PE Tablet – Fasted

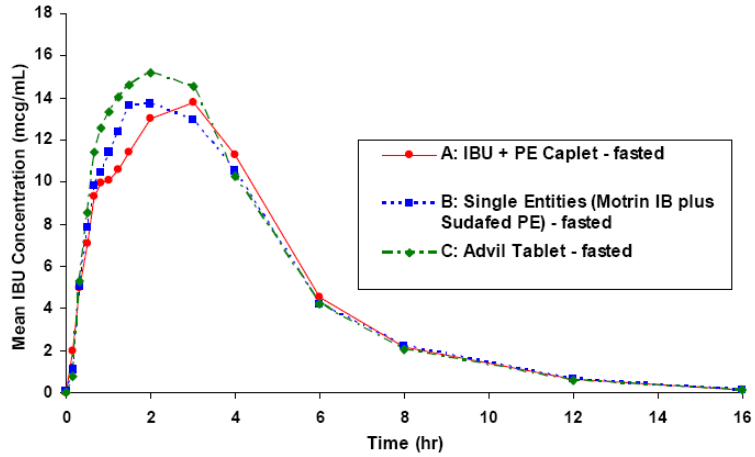


Figure 2.5.2.1 Mean IBU plasma concentration over time (Study AQ-08-12)

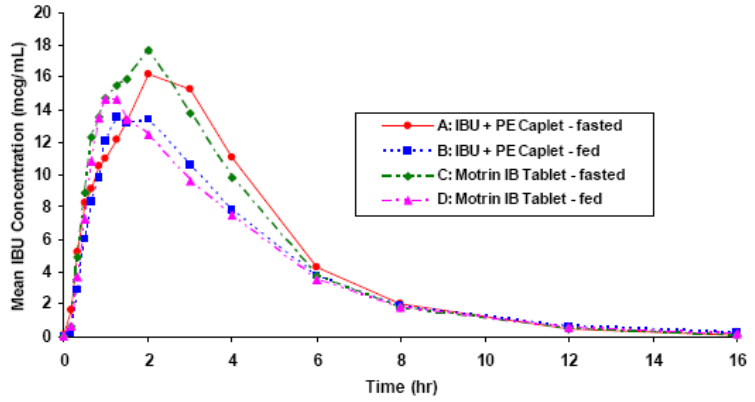


Figure 2.5.2.2 Mean IBU plasma concentration over time (Study AQ-08-13)

2.5.3 What is the likely clinical impact of delayed ibuprofen Tmax in the presence of PE?

Because no clinical trial was conducted with this new combination product of IBU and PE, the PK/PD models of ibuprofen for analgesic and antipyretic pain was used to help understand the likely impact of delayed Tmax of IBU for this combination product. See Appendix for Dr. Atul Bhattaram's Pharmacometrics review Appendix 4.3.

2.5.4 What is the effect of food on the bioavailability of the drug?

The 90% confidence interval (CI) for AUCL and AUCI for the comparison of IBU+PHE caplet under fed conditions vs. fasted conditions (B/A ratio) was within 80-125%; the 90% CI for Cmax (fed/fasted) was 79.8-96.1%, very close to the lower limit of 80% (Table 2.5.4.1). The mean Cmax of IBU (19.5 μg/mL) was comparable under fed and fasted condition [< 10% lower under fed condition than mean Cmax (21.2 μg/mL) under fasted condition]. Mean T_{max} values were higher under fasted compared to fed conditions.

Table 2.5.4.1 Mean (SD) IBU Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-13)

	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max}** (hr)
Mean (SD)				
A (n=42)	76.1 (15.7)	77.2 (15.7)	21.2 (5.6)	2.0 (0.5-6.0)
B (n=42)	63.3 (11.2)	65.9 (11.5)	19.5 (7.3)	1.4 (0.5-4.0)
C (n=42)	75.7 (14.5)	76.7 (14.5)	23.3 (5.6)	1.6 (0.5-4.0)
D (n=42)	62.3 (10.4)	63.7 (10.5)	20.3 (8.1)	1.1 (0.3-4.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/C*	100.4 (97.8-103.2)	100.6 (98.0-103.2)	91.2 (83.1-103.2)	—
B/D*	101.3 (98.7-104.1)	103.2 (100.5-105.9)	96.0 (87.5-105.2)	—
B/A*	83.5 (81.3-85.8)	85.8 (83.6-68.0)	87.6 (79.8-96.1)	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: IBU + PHE Caplet – Fed
C: Motrin IB Tablet – Fasted
D: Motrin IB Tablet – Fed

For phenyepherine, the 90% confidence interval (CI) for AUCL and AUCI for the comparison of IBU+PHE caplet under fed condition vs. fasted condition (B/A ratio) was within 80-125%; however, the 90% CI for Cmax (fed/fasted) was 66.3-91.3% (Table 2.5.4.2). The mean Cmax of free PE (695.1 μg/mL) was 22% lower under fed condition than mean Cmax (822.0 μg/mL)

under fasted condition. Median T_{max} values were lower under fasted compared to the fed condition (Figure 2.5.4.1).

Table 2.5.4.2 Mean (SD) Free PE Pharmacokinetic Parameters and Statistical Analysis (Study AQ-08-13)

	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max}** (min)
Mean (SD)				
A (n=42)	754.2 (188.0)	790.1 (193.7)	822.0 (336.8)	0.5 (0.2-0.8)
B (n=42)	824.8 (211.9)	854.6 (218.5)	695.1 (352.3)	0.8 (0.3-3.0)
E (n=42)	716.0 (196.3)	753.3 (200.1)	867.7 (560.8)	0.3 (0.2-1.0)
F (n=42)	828.9 (216.6)	864.8 (235.3)	819.4 (522.9)	0.7 (0.3-4.0)
Geometric Mean Ratio (%) (90% Confidence Intervals)^				
A/E*	106.7 (102.4-111.2)	106.2 (101.9-110.8)	100.9 (86.0-118.4)	—
B/F*	99.6 (95.5-103.8)	99.1 (95.1-103.3)	89.7 (76.4-105.3)	—
B/A*	108.2 (103.9-112.8)	107.0 (102.6-111.5)	77.8 (66.3-91.3)	—

*: Reference product ^: Based on fitted log-transformed parameters.
**: Median (range)
A: IBU + PHE Caplet – Fasted
B: IBU + PHE Caplet – Fed
E: Sudafed PE Tablet – Fasted
F: Sudafed PE Tablet – Fed

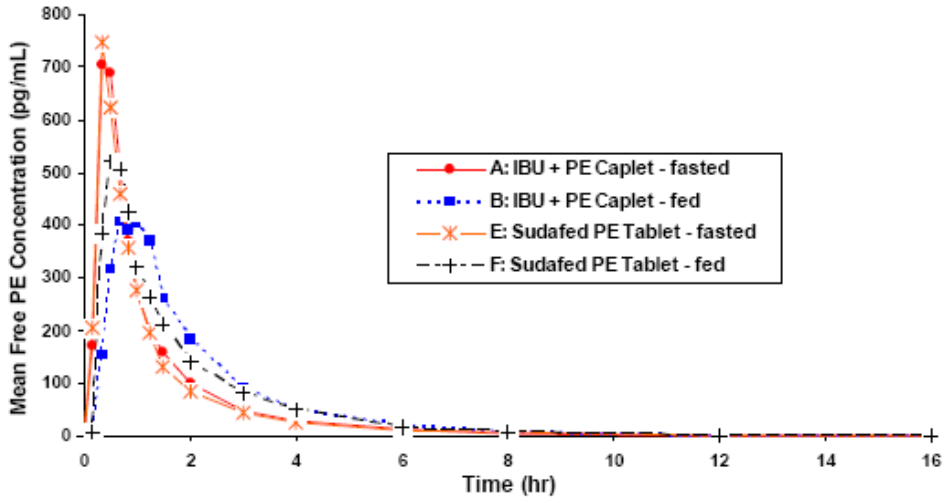


Figure 2.5.4.1 Mean Free PE plasma concentration over time (Study AQ-08-13)

In conclusion, there is some food effects observed: 1. The Cmax of PE in the test product is lower than the reference drug (Sudafed PE) under fed condition. 2. Cmax in fed condition is lower than that in fasted condition. Their clinical and labeling impact has been discussed in the

Office of Clinical Pharmacology Optional Intra-Divisional Briefing and NDA Wrap-up meeting, both held at different times on January 4, 2010. The clinical impact of this food effect is considered limited.

2.5.5 Was the to-be-marketed formulation studied in the pivotal PK study?

Yes. The final to-be-marketed formulation was the same as that used in the pivotal trials, Study AQ-08-12 and Study AQ-0813.

2.6 Analytical

2.6.1 Are the analytical and validation methods used to determine ibuprofen and phenylephrine acceptable?

Yes. The method is summarized in Table 2.6.1.1

For ibuprofen, briefly, a 100-µL sample aliquot is fortified with 25 µL of 25 µg/mL internal standard working solution and diluted with 100 µL of 0.1 M phosphoric acid. Analytes are isolated by a (b) (4). The organic layer is transferred to another 96-well plate and evaporated under a nitrogen stream at room temperature. The remaining residue is reconstituted with 250 µL of 0.01% formic acid in acetonitrile / 1.0 mM ammonium formate, 50:50 v/v. The final extract is analyzed via HPLC with MS/MS detection.

For free phenylepherine, briefly, a 250-µL sample aliquot is fortified with 50 µL of internal standard working solution and 100 µL of water. The analytes are isolated by (b) (4). Samples are washed with 400 µL of 25 mM citrate buffer followed by 400 µL of methanol and 400 µL of acetonitrile. The analytes are eluted with 300 µL of 2% formic acid in acetonitrile by centrifugation. The eluate is directly injected and analyzed via HPLC with MS/MS detection.

For total phenylepherine, briefly, a 50.0-µL sample aliquot is fortified with 50 µL of phenylephrine-d3 internal standard working solution and 100 µL of a β-glucuronidase/sufatase solution prepared in 200 mM ammonium acetate, pH 4.5, buffer. The samples are then incubated overnight (up to 20 hours) at 37 °C. The analytes are isolated by weak cation-exchange solid phase extraction using 10-mg Phenomenex Strata-X CW 96-well plates. Samples are washed with 400 µL of 25 mM citrate buffer followed by 400 µL of methanol and 400 µL of acetonitrile. The analytes are eluted with 500 µL of 2% formic acid in acetonitrile by centrifugation. The eluate is injected directly and analyzed via HPLC with MS/MS detection in positive ion electrospray mode using a Sciex API 3000 equipped with an Ionics HSID interface. For multiple reactions monitoring (MRM), the monitored transitions are m/z 168.1 to 150.1 for phenylephrine and m/z 171.1 to 153.1 for phenylephrine-d3.

The method is adequately validated to show selectivity and sensitivity. The performance was acceptable (Table 2.6.1.2). The DSI inspection did not identify issues.

Table 2.6.1.1 Summary of Analytical Method for Ibuprofen, free PE and Total PE.

Analytes	Matrix	Internal Standard	Analytical Method	QC Samples	LOQ	Linear Range	Long-Term Stability in plasma at -20ºC
Ibuprofen	Plasma	(b) (4)	(b) (4) Method LCMSB 409 V 1.01	0.2, 0.5, 1.0, 3.0, 10 and 37.5 µg/mL	0.2 µg/mL	0.2-50 µg/mL	266 days (-70 °C)
Phenylephrine	Plasma	(b) (4)	(b) (4) Method LCMSC 392.1 V2	10, 25, 50, 150, 500, and 1900 pg./mL	10 pg/mL	10.0-2500 pg/mL	572 days (2-8 °C) 399 days (-70 °C)
Total Phenylephrine	Plasma	(b) (4)	(b) (4) Method LCMS 257 V 3.01	1, 3, 8, 30, 125, and 750 ng/mL	1.00 ng/mL	1.0-1000 ng/mL	276 days (-70 °C)

Table 2.6.1.2 Assessment of accuracy and precision of assay methodologies for IBU, free PE and Total PE (HPLC)

	Analyte		
	IBU	Free PE	Total PE
Intra-Assay Accuracy	-5.10% to 6.92%	-5.21% to 5.10%	-13.3% to 0.22%
Intra-Assay Precision	0.54% to 3.36%	1.57% to 7.19%	1.10% to 5.24%
Inter-Assay Accuracy	-5.17% to 4.21%	-2.04% to 3.74%	-10.8% to -1.75%
Inter-Assay Precision	1.11 to 2.79%	2.81% to 6.06%	2.19% to 6.11%
Lower Limit of Quantitation	0.200mcg/mL	10 pg/mL	1.00 ng/mL

3 LABELING RECOMMENDATIONS

The label for an OTC product generally does not contain extensive clinical pharmacology information. The labeling impact regarding the food effect on phenylephrine has been discussed in the Office of Clinical Pharmacology Optional Intra-Divisional Briefing and NDA Wrap-up meeting, both held on January 4, 2010. Sponsor's proposed labeling language "take with food or milk if stomach upset occurs" is acceptable from clinical pharmacology perspective. Please refer to the appropriate reviews from ONP/DNCE for details of labeling review comments.

3 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

4.2 OCP Filing and Review Form

Office of Clinical Pharmacology New Drug Application Filing Form			
General Information About the Submission			
	Information		Information
NDA Number	**22-565**	**Brand Name**	**Advil Cold & Sinus PE Caplets**
OCP Division	**DCP2**	**Generic Name**	**Ibuprofen/Phenylephrine HCl**
Medical Division	**ONP**	**Drug Class**	
OCP Reviewer	**Ying Fan**	**Proposed Indication(s)**	**Temporary relief of the symptoms associated with the common cold or flu for age 12 and above**
OCP Team Leader (acting)	**Dakshina Chilukuri**	**Dosage Form**	**Caplets, 200 mg Ibuprofen/10 mg Phenylephrine**
		Dosing Regimen	**Take 1 caplet every 4 hours while symptoms persist, do not use more than 6 caplets in any 24 hour period unless directed by a doctor**
Date of Submission	**7/28/ 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**2/14/2010**	**Sponsor**	**Wyeth Consumer Healthcare**
PDUFA Due Date	**5/28/2010**	**Priority Classification**	**Standard**
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**			**AQ-08-12, AQ-06-08**
multiple dose:				
Patients-				
single dose:	x			**AQ-08-13**
multiple dose:				
Dose proportionality -				

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**x**			**AQ-08-12, AQ-08-13**
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**			**AQ-08-12, AQ-08-13 and AQ-06-08**
replicate design; single / multi dose:				
Food-drug interaction studies:	**x**			**AQ-08-13**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?				
QBR questions (key issues to be considered)	**Are the analytical and validation methods used acceptable?** **Is the potential impact of delayed Tmax in the presence of phenylephrine, and lower Cmax under fed condition on clinical efficacy addressed?** **Is there any drug-drug interaction between the Ibuprofen and Phenylephrine?** **Is there any food effect?**			

4.3 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

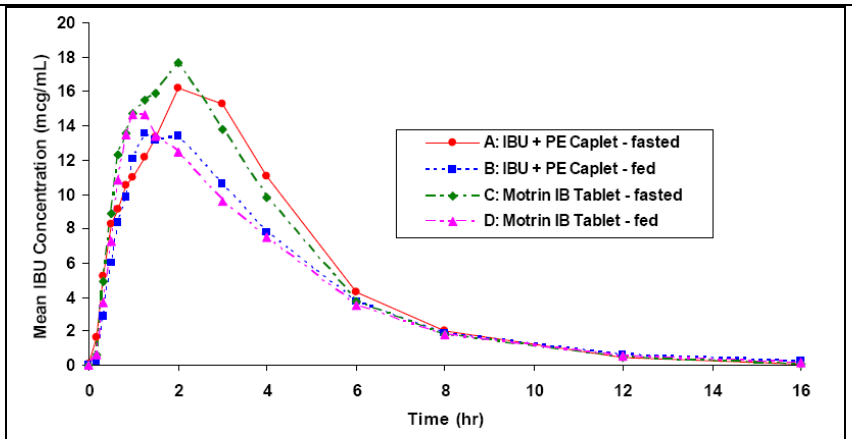
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

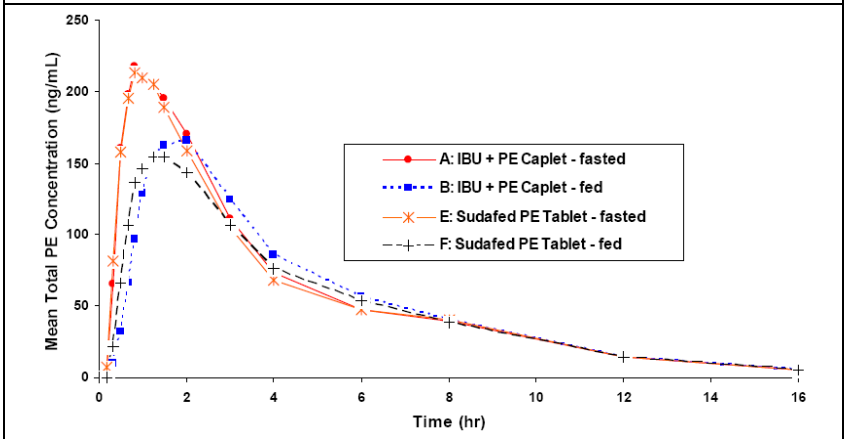
1.1.1 Is there a delay in the onset of analgesic efficacy due to delayed Ibuprofen (IBU) Tmax (by 30 minutes) of the Ibuprofen/Phenylephrine (IBU/PE) formulation?

Unlikely. Figure 1 shows the PK profile of Ibuprofen (IBU), Phenylephrine (PE) from IBU/PE formulation in comparison to single ingredient Motrin IB (200 mg) and to Sudafed PE (PE 10 mg) from Study AQ-08-13.

Figure 1. (A) Mean IBU Plasma Concentration (B) Mean PE Plasma Concentration over Time (Study AQ-08-13).



(A)



(B)

Table 1 shows the summary of PK parameters based on non-compartmental analysis.

Table 1. Summary of PK parameters of Ibuprofen and Phenylephrine from Study AQ-08-13.

Treatment	AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	C_{max} (mcg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
A[#]	76.1 (15.7)	77.2 (15.7)	21.2 (5.6)	131.4 (62.6)	2.0 (0.3)
B	63.3 (11.2)	65.9 (11.5)	19.5 (7.3)	97.5 (56.2)	2.8 (2.3)
C	75.7 (14.5)	76.7 (14.5)	23.3 (5.6)	99.8 (48.8)	2.0 (0.3)
D	62.3 (10.4)	63.7 (10.5)	20.3 (8.1)	92.5 (62.6)	2.2 (0.6)
Ratio (90% CI) ^					
A/C* %	100.4 (97.8-103.2)	100.6 (98.0-103.2)	91.2 (83.1-103.2)	___	___
B/D* %	101.3 (98.7-104.1)	103.2 (100.5-105.9)	96.0 (87.5-105.2)	___	___
B/A* %	83.5 (81.3-85.8)	85.8 (83.6-88.0)	87.6 (79.8-96.1)	___	___

* Reference product
^ Based on fitted log-transformed parameters.
A: IBU+PE Caplet – fasted; B: IBU+PE Caplet – Fed; C: Motrin IB Tablet – fasted; D: Motrin IB Tablet –fed
Subject No. 212 withdrew voluntarily before period 6. The treatment assigned for this period was A. Consequently, the summary statistics, ratio, and 90% CI for all PK parameters for treatment A were based on 41 subjects.

Treatment	AUCL (pg•h/mL)	AUCI (pg•h/mL)	C_{max} (pg/mL)	T_{max} (min)	$t_{½}$ (h)
Mean (SD)					
A[#]	754.2 (188.0)	790.1 (193.7)	822.0 (336.8)	26.2 (7.3)	1.7 (1.1)
B	824.8 (211.9)	854.6 (218.5)	695.1 (352.3)	67.0 (43.0)	1.4 (0.9)
E	716.0 (196.3)	753.3 (200.1)	867.7 (560.8)	26.5 (11.9)	1.8 (1.2)
F[@]	828.9 (216.6)	864.8 (235.3)	819.4 (522.9)	60.6 (49.3)	1.6 (1.1)
Ratio (90% CI) ^					
A/E* %	106.7 (102.4-111.2)	106.2 (101.9-110.8)	100.9 (86.0-118.4)	___	___
B/F* %	99.6 (95.5-103.8)	99.1 (95.1-103.3)	89.7 (76.4-105.3)	___	___
B/A* %	108.2 (103.9-112.8)	107.0 (102.6-111.5)	77.8 (66.3-91.3)	___	___

* Reference product
^Based on fitted log-transformed parameters.

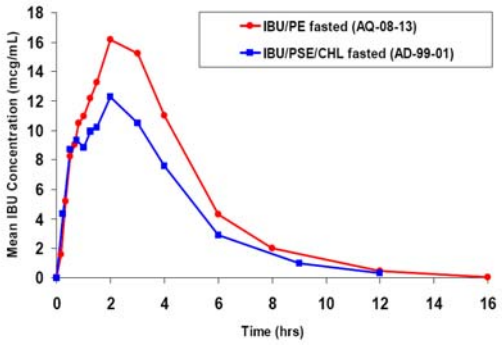
As shown in Table 1, the mean difference in Tmax of Ibuprofen from IBU/PE formulation in comparison to Motrin IB tablet was 27.5 min (p=0.061). In another study (AQ-08-12) the mean difference in Tmax of Ibuprofen from IBU/PE formulation in comparison to single ingredient Advil (IBU 200 mg) was 30 min (p=0.024).

Sponsor provided the following rationale for the likely lack of delay in the onset of analgesic efficacy due to a delay in Tmax of Ibuprofen from the IBU/PE formulation:

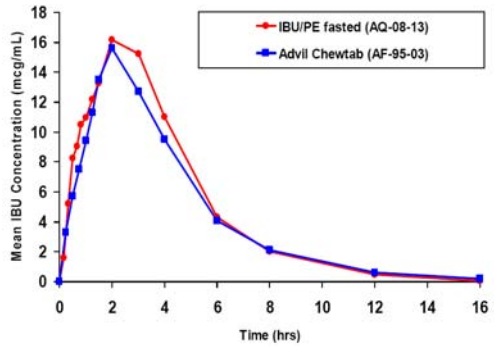
1. Adequate analgesia has been shown by IBU containing products with pharmacokinetic (PK) profile similar to that of IBU from IBU/PE formulation. The sponsor summarized data from (A) Advil® Allergy Sinus, NDA 21-441 (B) Advil Chew Tabs, NDA 20-994 (C)Advil PM Caplets, NDA 21-394 and (D) Motrin Chew Tab, NDA 20-135.

Figure 2 shows that the PK profile of Ibuprofen from IBU/PE formulation in this submission is similar in shape to other approved formulations containing Ibuprofen.

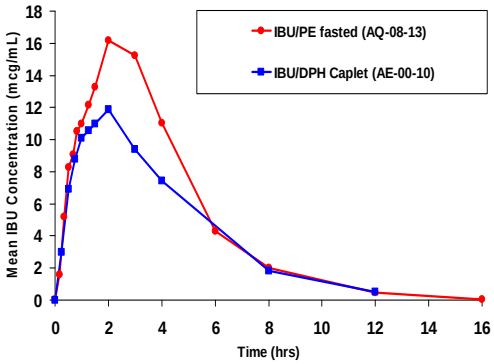
Figure 2. PK profile of Ibuprofen from (A) Advil® Allergy Sinus, NDA 21-441 (B) Advil Chew Tabs, NDA 20-994 (C) Advil PM Caplets, NDA 21-394.



(A)



(B)



(C)

The Tmax of Ibuprofen from other approved formulations is shown in Table 2.

Table 2. Summary of Tmax of Ibuprofen from various approved formulations.

NDA/Study	Formulation	Tmax of Ibuprofen (min)
21-441/AD-99-01	Advil Multi-Symptom Allergy Sinus (IBU/PSE/CHL)	110
20-994/AF-95-03	Advil Chewable Tables	112
20-135/125	Motrin Chew Tablets	117
21-394/AE-00-10	Advil PM Caplets	131

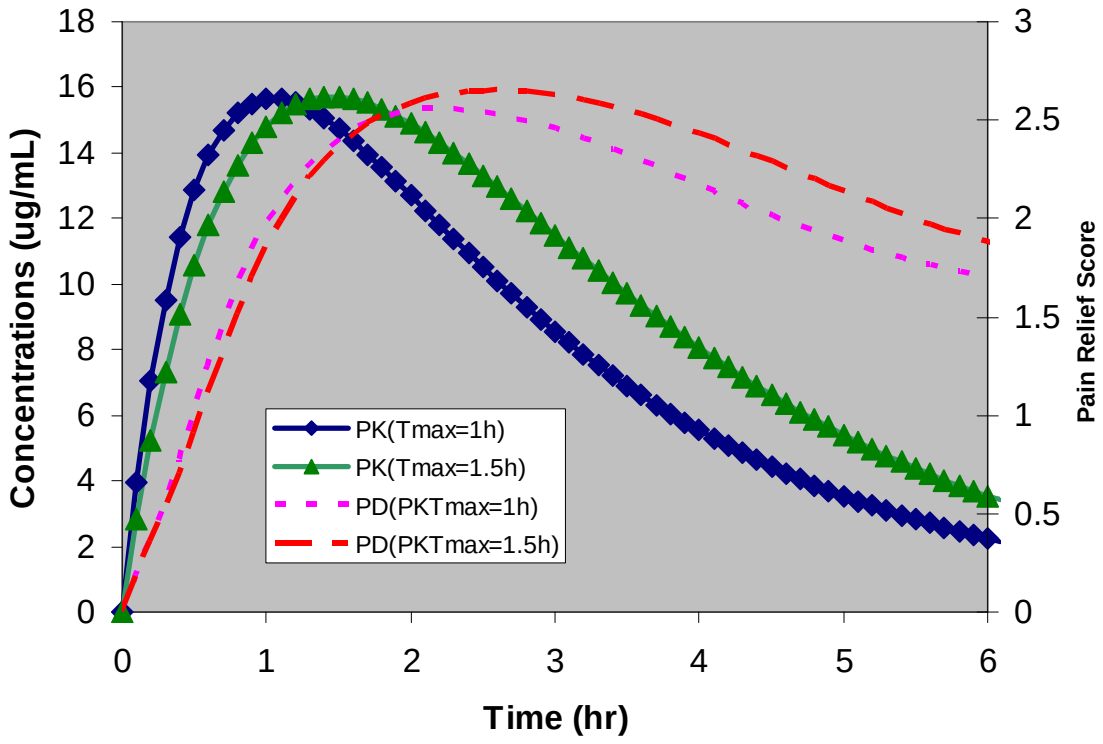
Sponsor also conducted PK/PD analysis using pain relief, risk of remedication, time to meaningful pain relief and time to first perceptible pain relief as pharmacodynamic endpoints. The pharmacodynamic endpoints were derived from a study, in dental patients after third molar extraction, conducted to investigate whether the faster

absorption of ibuprofen translates to faster pain relief (Protocol AI-07-02). In this study, approximately 280 subjects were randomized to treatment with aspirin, standard ibuprofen tablets (Nurofen® , 2 x 200 mg), IBU effervescent tablets (1 x 400 mg), or placebo (2:2:2:1). PKPD data were collected for approximately 25 subjects receiving standard ibuprofen, and 25 subjects receiving effervescent ibuprofen. Placebo data was available for approximately 40 subjects.

The reviewer conducted simulations using the estimated PK-PD with Berkeley Madonna® to evaluate the impact of delay in Tmax on pain relief.

Figure 3 shows the time course of plasma concentrations of ibuprofen from two formulations with Tmax of 1 h and 1.5 h. The difference in Tmax reflects the reported differences in Tmax of ibuprofen by 0.5 h between IBU/PE and other formulations. The differences in Tmax do not appear to translate into major differences in pain relief score.

Figure 3. Mean time course of plasma ibuprofen concentrations and pain relief from two formulations with Tmax of 1h and 1.5h.



1.2 Recommendations

The differences in Tmax of ibuprofen from IBU/PE and other approved formulations do not appear to translate into major differences in pain relief score. Also the observed Tmax of ibuprofen from IBU/PE formulation is in similar range to other formulations as shown in Table 1.

1.3 Label Statements

NA

2 PERTINENT REGULATORY BACKGROUND

Wyeth Consumer Healthcare (WCH) intends to offer Advil Cold & Sinus PE (IBU/PE) as an over-the-counter (OTC) alternative to the pseudoephedrine product Advil Cold and Sinus (NDA 19-771), which was moved behind-the-counter in compliance with legislation restricting the sale of all pseudoephedrine-containing drug products (The Combat Methamphetamine Epidemic Act of 2005). Sponsor compared the PK of Ibuprofen and Phenylephrine from the IBU/PE formulation and other approved products. The PK studies showed that the Tmax of ibuprofen from IBU/PE formulation was delayed by 30 min when compared to other formulations (Motrin, Sudafed). FDA asked WCH to provide adequate clinical data to support that there is no delay in the onset of analgesic efficacy due to the delayed IBU T_{max} of the IBU/PE formulation. FDA also indicated that WCH could reference other ibuprofen products with a PK profile similar to that of Advil C&S PE which had been demonstrated to provide adequate analgesic effect.

3 RESULTS OF SPONSOR'S ANALYSIS

WCH developed a 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). Simulation of TMPR and TFPR was performed using the PK model parameters for effervescent ibuprofen and standard ibuprofen tablets from study AI-07-02, a study in dental patients after molar extraction. An objective of the analysis was to establish the IBU exposure-response relationship of TMPR and TFPR by using the PK and PD results from the study. PK and PD data were collected from a subset of the population consisting of 37 patients in the placebo group, 30 patients in the IBU effervescent group and 22 patients in the standard ibuprofen tablet group. Plasma ibuprofen samples were collected at pre-dose, 0.167, 0.25, 0.33, 0.417, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours post-dose. Pain relief and pain intensity scores were measured at baseline, at 0.25, 0.5, 0.75, 1 and 1.5 hr post-dose, and then hourly until 8 hours post-dose. TFPR and TMPR were measured using the double stopwatch method. Patients were encouraged to postpone remedication until after one hour post-dose. Plasma ibuprofen concentration time course data were analyzed by nonlinear mixed effects modeling. The effect of ibuprofen plasma concentration on TMPR, TFPR was evaluated using hazard models. These models were developed and examined using the S-plus 6.2 program (Insightful Corp., Seattle, Washington).

Figure 4 shows the shows the mean plasma ibuprofen concentration of patients treated with 400 mg effervescent ibuprofen tablets or standard ibuprofen tablets. Absorption of effervescent ibuprofen is faster than standard ibuprofen. Tmax of effervescent ibuprofen group is approximately 0.33 hr, which is much shorter than the 1.5 hour for the standard ibuprofen group. Mean maximum plasma ibuprofen concentration (Cmax) of effervescent ibuprofen group is 45.7 $\mu g.mL^{-1}$, which is almost twice the 25.9 $\mu g.mL^{-1}$ for standard ibuprofen group. The estimates of the pharmacokinetic parameters are shown in Table 3.

Figure 4. Mean (±95% CI) plasma ibuprofen concentrations of patients treated with 400 mg effervescent ibuprofen tablets (IBU eff) or standard ibuprofen tablets (IBU Nurofen).

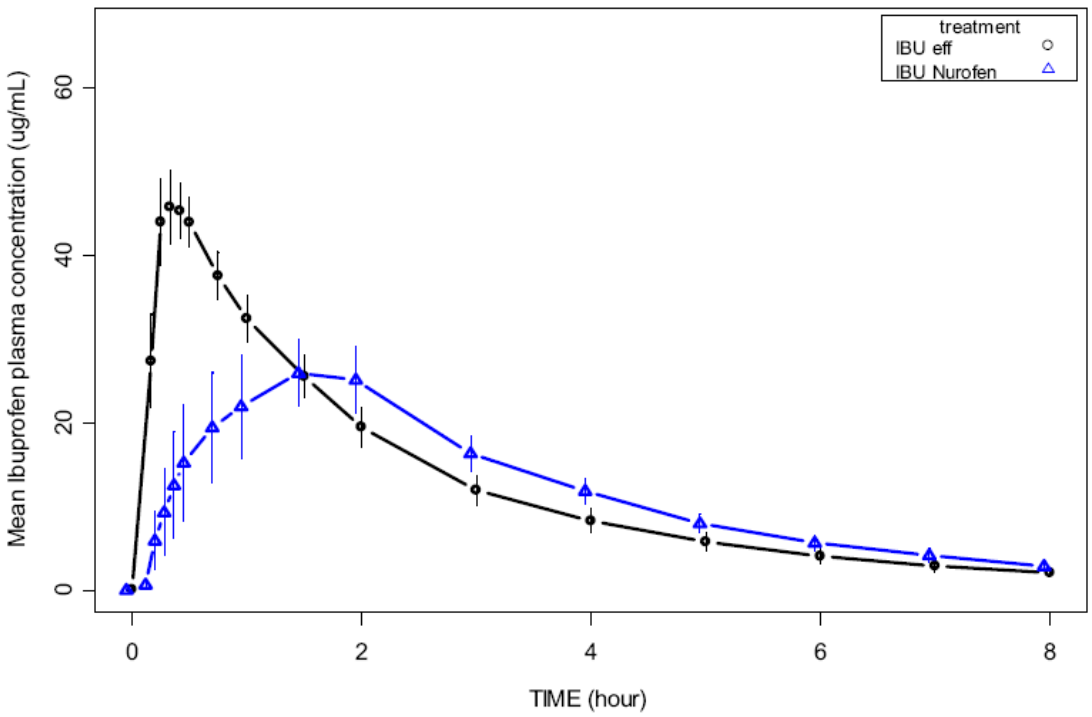


Table 3 Typical pharmacokinetic parameters and 90% confidence intervals of estimates of (A) Effervescent (B) Standard ibuprofen tablet.

Parameters	Estimate	SE	90% CI
Ka (1/hr)	23.7	0.19 *	[18.4, 30.3]**
Tlag (hr)	0.140	0.009 *	[0.138, 0.142]**
V/F (L)	7.45	0.030 *	[7.17, 7.75]**
CL (L/hr)	3.77	0.064 *	[3.46, 4.10]**
$\omega^2_{log(ka)}$	1.4E-12		
$\omega^2_{log(Tlag)}$	0.50		
$\omega^2_{log(V/F)}$	0.024		
$\omega^2_{log(CL)}$	0.095		
σ^2	1.66		

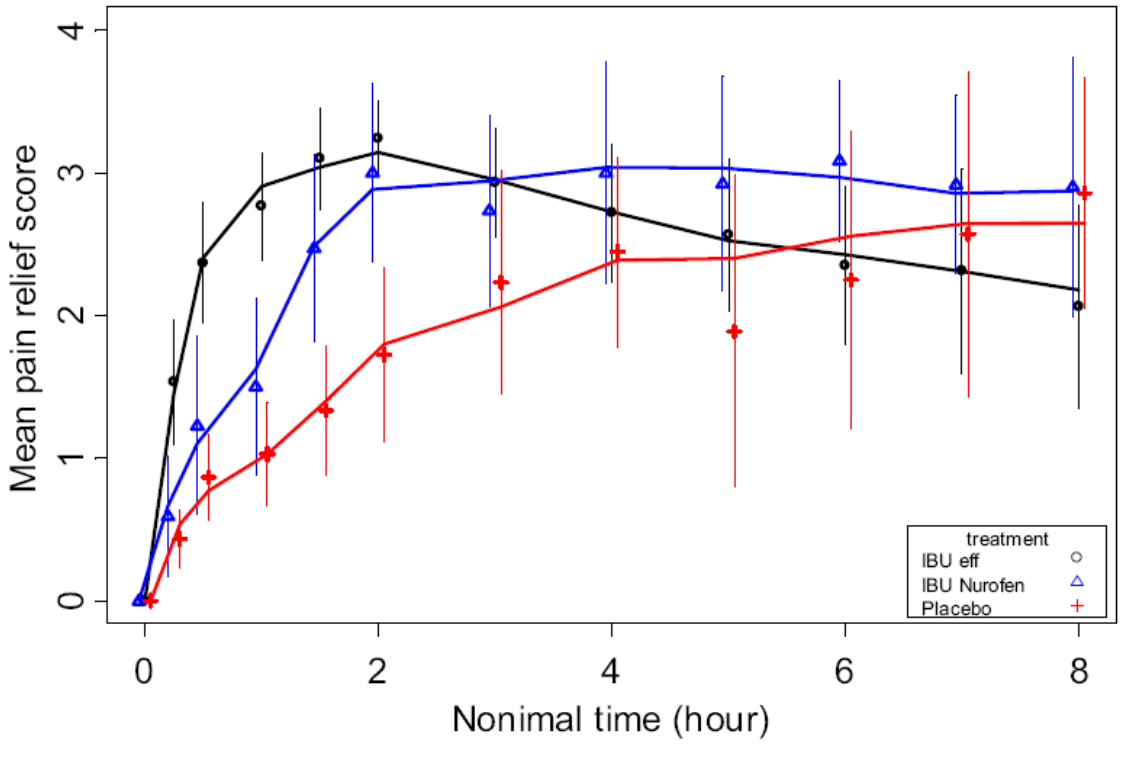
(A)

Parameters	Estimate	SE	90% CI
Ka (1/hr)	1.78	0.24 *	[1.19, 2.66]**
Tlag (hr)	0.33	0.16 *	[0.26, 0.42]**
V/F (L)	8.12	0.071 *	[7.20, 9.14]**
CL (L/hr)	3.66	0.068 *	[3.26, 4.10]**
$\omega^2_{log(ka)}$	1.14		
$\omega^2_{log(Tlag)}$	0.50		
$\omega^2_{log(V/F)}$	0.051		
$\omega^2_{log(CL)}$	0.046		
σ^2	2.66		

(B)

Figure 5 shows the observed and model fitted pain relief score for patients treated with placebo, efferverscent or standard ibuprofen tablets.

Figure 5. Mean observed and model fitted pain relief score for patients treated with placebo, effervescent ibuprofen or standard ibuprofen. Symbols represent the mean observed pain relief score and the error bars represents 95% confidence interval. Solid lines represent the mean of model predicted values.



The estimates of the PK-PD parameters are shown in Table 4.

Table 4. Pain relief model parameters and 95% confidence intervals.

Parameter	Estimated	SE	95% CI
P_{max} (PR units)	1.54	0.12	[1.30, 1.77]
K (hr^{-1})	1.26	0.056*	[1.13, 1.41] **
K_{eo} (hr^{-1})	1.49	0.207*	[0.99, 2.23]**
E_{max} (PR units)	1.80	0.237	[1.33, 2.26]
EC_{50} ($\mu g \cdot mL^{-1}$)	10.2	0.225*	[6.6, 15.8]**
R	2.0	0.434	[1.2, 2.9]
ω^2_{pmax}	1.30		
$\omega^2_{log(k)}$	3.76		
$\omega^2_{log(keo)}$	0.73		
ω^2_{Emax}	1.11		
σ^2	0.26		

* SE of the log-transformed parameters
** Based on a backward transformation of the log scale confidence interval
ω^2 are the variances of the random effect of the parameters
σ^2 is the variance of the model residual

Reviewer's Comments: The PK-PD analysis methodology conducted by the sponsor is acceptable. However, one should note that the PK-PD model was developed in a subset of total population and using only available data (not complete data from all patients due to drop-outs).

4 REVIEWER'S ANALYSIS

NA

4.1 Introduction

NA

4.2 Objectives

NA

4.3 Methods

4.3.1 Data Sets

NA

4.3.2 Software

NA

4.3.3 Models

NA

4.4 Results

NA

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Painrelief.ctl	NONMEM code for effect compartment model	Z:\Ibuprofen_Phenylyephrine_NDA22565_VAB\ER Analyses\PDAnalysis
panrelief nm.input.csv	NONMEM dataset	Z:\Ibuprofen_Phenylyephrine_NDA22565_VAB\ER Analyses\PDAnalysis
Ibuprofen pkpd modeling v1.3.txt	SPLUS code for nonlinear mixed effects analysis of PK and time to event analysis (REMD, TMPR, TFPR)	Z:\Ibuprofen_Phenylyephrine_NDA22565_VAB\Sponsor Data and Reports
PainRelief_Ibuprofen mmd	Berkeley Madonna Simulation Code for Pain Relief	Z:\Ibuprofen_Phenylyephrine_NDA22565_VAB\ER Analyses\PDAnalysis

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22565	ORIG-1	WYETH CONSUMER HEALTHCARE	ADVIL COLD & SINUS PE(IBUPROFEN 200MG/PH

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

/s/

YING FAN
01/14/2010

VENKATESH A BHATTARAM
01/14/2010

YANING WANG
01/14/2010

PARTHA ROY
01/14/2010

Office of Clinical Pharmacology

New Drug Application Filing Form

General Information About the Submission

	Information		Information
NDA Number	**22-565**	**Brand Name**	**Advil Cold & Sinus PE Caplets**
OCP Division	**DCP2**	**Generic Name**	**Ibuprofen/Phenylephrine HCl**
Medical Division	**ONP**	**Drug Class**	
OCP Reviewer	**Ying Fan**	**Proposed Indication(s)**	**Temporary relief of the symptoms associated with the common cold or flu for age 12 and above**
OCP Team Leader (acting)	**Dakshina Chilukuri**	**Dosage Form**	**Caplets, 200 mg Ibuprofen/10 mg Phenylephrine**
		Dosing Regimen	**Take 1 caplet every 4 hours while symptoms persist, do not use more than 6 caplets in any 24 hour period unless directed by a doctor**
Date of Submission	**7/28/ 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**2/14/2010**	**Sponsor**	**Wyeth Consumer Healthcare**
PDUFA Due Date	**5/28/2010**	**Priority Classification**	**Standard**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
1 Healthy Volunteers-				
single dose:	**x**			**AQ-08-12, AQ-06-08**
multiple dose:				
2 Patients-				
single dose:	x			**AQ-08-13**
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**x**			**AQ-08-12, AQ-08-13**
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**			**AQ-08-12, AQ-08-13 and AQ-06-08**
replicate design; single / multi dose:				
Food-drug interaction studies:	**x**			**AQ-08-13**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		
3				

4 Filability and QBR comments		
5	**"X" if yes**	**6 Comments**
Application filable?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		
QBR questions (key issues to be considered)	**Are the analytical and validation methods used acceptable?** **Is the potential impact of delayed Tmax in the presence of phenylephrine, and lower Cmax under fed condition on clinical efficacy addressed?** **Is there any drug-drug interaction between the Ibuprofen and Phenylephrine?** **Is there any food effect?**	

Introduction

The sponsor Wyeth Consumer Healthcare (WCH) is submitting a 505 (b)(2) new drug application (NDA) for a new combination of ibuprofen (IBU) (200 mg) and phenylephrine (PE) (10 mg) to provide an alternative to the ibuprofen (200 mg)/pseudoephedrine HCl (30 mg) product currently marketed under the trade name Advil Cold & Sinus (NDA 19-771) with the indication of temporary relief of symptoms associated with the common cold or flu for age 12 and above.

The combination of the over-the-counter (OTC) analgesic ibuprofen (IBU) with the nasal decongestant pseudoephedrine hydrochloride (PSE) was approved as a solid dosage form in 1989 (NDA19-771), as a suspension in 2002 (NDA 21-373) and as a liquid-filled capsule in 2002 (NDA 21-374). The solid oral dosage form product is being reformulated with the substitution of phenylephrine hydrochloride (PE) for PSE. This reformulation is to decrease the availability of PSE-containing products and thus decrease the opportunity for illicit conversion of PSE to methamphetamine.

Wyeth Consumer Healthcare (WCH) intends to offer Advil Cold & Sinus PE (IBU/PE) as an over-the-counter (OTC) alternative to the pseudoephedrine product Advil Cold and Sinus (NDA 19-771), which was moved behind-the-counter in compliance with legislation restricting the sale of all pseudoephedrine-containing drug products (The Combat Methamphetamine Epidemic Act of 2005).

The sponsor (Wyeth Consumer Healthcare) received a Not Approvable (NA) letter for NDA 22-112 on May 7, 2008. The reason of the NA letter in Clinical Pharmacology perspective is: 1) The submitted PK data for phenylephrine are unreliable due to major flaws in the analytical assay methodology. 2) A cross-study comparison of ibuprofen PK data from Study AQ-05-03 to the historical ibuprofen PK data suggests that the mean Tmax values of ibuprofen increased approximately 0.6 hr in the presence of phenylephrine. In addition, a lower ibuprofen Cmax value was observed under fed conditions compared to fasting conditions.

In response to that, in current submission (NDA 22-565), the sponsor conducted new three pharmacokinetic (PK) studies to address the deficiencies communicated to them in the NA letter.

The Filing meeting for this submission was held on September 22, 2009.

Biopharmaceutics Program:
WCH initially conducted study AQ-05-03 to support this product (NDA 22-112). Subsequent to completing study AQ-05-03, WCH discovered through routine formula optimization activities that the addition of an antioxidant preservative, 0.25% propyl gallate (PG), reduced the level of an oxidative degradant (PE ketone) below that of the ICH threshold (0.5%). Accordingly, WCH conducted PK study, AQ-06-08, a study designed as a bridge between the IBU/PE formula studied in AQ-05-03 and the formula intended for commercialization. The difference between the two formulas involved the

addition of PG. In study AQ-06-08, the sponsor indicated that two products were bioequivalent for IBU with a T_{max} of 1.60 and 1.66 hours, for the non-PG and PG formulations, respectively. The sponsor also stated that the PE results were considered flawed because of a methodological issue with the assay. The flawed assay measured total PE (conjugated plus unconjugated PE) and was used in studies AQ-05-03 and AQ-06-08.

Clinical Pharmacology Program:
As previously mentioned, the initial clinical pharmacology study AQ-05-03 was submitted in NDA 22-112. In its review of the application, FDA determined that the PK data for total PE was unreliable based on a flaw in the analytical assay methodology. Further, the Agency recommended that WCH submit PK data using an adequately validated assay for quantifying unmetabolized (free) PE in plasma. Additionally, the Agency requested that WCH address the potential impact on clinical efficacy of delayed IBU T_{max} in the presence of PE and lower IBU C_{max} under fed conditions.

In response, WCH conducted two PK studies, AQ-08-12 and AQ-08-13, using the final formulation. These two studies investigated drug interactions, formulation effects and foods effects. A new and validated assay that measures free PE was employed in these two studies. In addition, samples were also assayed for total PE using a revised and re-validated total PE assay. This revised and revalidated assay was different from the one used in studies AQ-05-03 and AQ-06-08.

Study AQ-08-12 characterized the rate and extent of IBU and PE absorption from IBU/PE 200/10 mg caplets compared to marketed Motrin IB (IBU 200 mg) and Sudafed PE (PE 10 mg) single entity products administered concomitantly and to Advil (IBU 200 mg) administered alone.
Sponsor conclusion:
IBU/PE had an equivalent rate and extent of IBU and PE absorption relative to the single entity products, Motrin IB and Sudafed PE, when administered concomitantly. The IBU T_{max} estimated difference in the comparison of IBU/PE versus Motrin IB + Sudafed PE was 23 minutes, but this difference was not statistically significant (p=0.169). IBU/PE was also bioequivalent (BE) to single entity Advil tablets, indicating that the combination had an equivalent rate and extent of IBU absorption. The IBU T_{max} for the combination was longer by 30 minutes compared to Advil tablets (p=0.024).

Study AQ-08-13 characterized, under fasted conditions, the rate and extent of IBU and PE absorption from IBU/PE 200/10 mg caplets compared to single ingredient Motrin IB (IBU 200 mg) and to Sudafed PE (PE 10 mg) administered alone. It further characterized the rate and extent of IBU and PE absorption from IBU/PE administered under fed conditions to that of Motrin IB and Sudafed PE administered individually under fed conditions.
Sponsor conclusion:
The results showed that under fasted conditions, IBU/PE was BE to Motrin IB and Sudafed PE for AUC and C_{max}. T_{max} of the combination caplet was achieved 28 minutes later than for Motrin IB, but this difference was not statistically significant, p=0.061.

Under fed conditions, IBU/PE was bioequivalent (BE) to Motrin IB for AUC and C_{max} and BE to Sudafed PE for AUC. The lower bound of the 90% confidence interval for C_{max} in the free PE assay was outside the limits for BE, 76%.

IBU T_{max}

WCH met with the Agency on December 2, 2008 to discuss the results of studies AQ-08-12 and AQ-08-13. The Agency asked WCH to provide adequate clinical data to support that there is no delay in the onset of analgesic efficacy due to the delayed IBU T_{max} of the IBU/PE formulation. The Agency also indicated that WCH could reference other ibuprofen products with a PK profile similar to that of Advil C&S PE which had been demonstrated to provide adequate analgesia (defined as onset of analgesia within one hour).

The sponsor provided four examples of IBU containing products with PK profiles similar to that of IBU/PE and that have been shown to provide adequate analgesia. The four examples consist of IBU products with T_{max} ranging between 110-131 minutes (the mean T_{max} of IBU/PE was 131 minutes). Additionally, the four products have been shown to be effective within one to two hours by different measures including pain intensity difference scores, fever reduction, sleep latency (a known surrogate of pain relief) and the proportion of subjects requiring rescue medication within 1-2 hours after dosing.

Additionally, WCH has recently developed a pharmacokinetic/ pharmacodynamic (PK/PD) model for predicting IBU onset of analgesia based on T_{max} and C_{max}. The model was developed with data from a study involving different dosage forms of IBU for the treatment of postoperative molar impaction pain. The study evaluated the relationship between IBU pharmacokinetics and onset of analgesic effect, as determined by time to first perceptible relief and time to meaningful relief. Based on the IBU C_{max} and T_{max} of the IBU/PE formulation, the model predicts that the IBU/PE formulation will provide adequate onset of analgesic effect.

Reviewer's Comments:

1. The Division of Clinical Pharmacology 2 (DCP2) has reviewed this NDA for filing purpose. This NDA is fileable from a clinical pharmacology perspective.
2. DSI inspection will be requested.
3. Pharmacometrics consult request has been issued.

QBR questions:

Are the analytical and validation methods used acceptable?

Is the potential impact of delayed T_{max} in the presence of phenylephrine, and lower C_{max} under fed condition on clinical efficacy addressed?

Is there any drug-drug interaction between the Ibuprofen and Phenylephrine?

Is there any food effect?

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

/s/

YING FAN
10/07/2009

DAKSHINA M CHILUKURI
10/07/2009