

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022113Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

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| NDA 22-113: | Submission Date: June 21, 2011 |
| Generic Name: | Ibuprofen / Phenylephrine / Chlorpheniramine |
| Brand Name: | (b) (4) |
| Reviewer: | Partha Roy, Ph.D. |
| Team Leader (Acting): | Suresh Doddapaneni, Ph.D. |
| OCP Division: | Clinical Pharmacology 2 (DCP2) |
| OND Division: | DNCE/ONP |
| Sponsor: | Pfizer Consumer Healthcare (formerly Wyeth) |
| Submission Type: | Resubmission |
| Formulation; Strength(s): | Caplets; Ibuprofen 200 mg / Phenylephrine HCl 10 mg / Chlorpheniramine Maleate 4 mg |
| Indications: | Temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor body aches and pains, fever. |

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1 EXECUTIVE SUMMARY

1.1 Recommendations

From Clinical Pharmacology perspective, NDA 22-113 is acceptable provided that the audit of study AD-08-10 by the Office of Scientific Inspections (OSI) does not identify any significant issues precluding the acceptance of data.

1.2 Phase 4 Commitments

None

1.3 Background

This NDA re-submission constitutes a complete response to a Not Approval Action Letter dated July 25, 2008 pertaining to a 505 (b)(2) NDA application for a new triple combination of ibuprofen (IBU) (200 mg), phenylephrine (PE) (10 mg) and chlorpheniramine (CHLOR)(4 mg) that provides an alternative to the ibuprofen (200 mg)/pseudoephedrine HCl (30 mg)/chlorpheniramine (2 mg) product currently marketed under the trade name Advil Allergy Sinus caplets (NDA 21-441) as a combination pain reliever/fever reducer, nasal decongestant and antihistamine for ages 12 years and above. It is noted that the dose of CHLOR has been adjusted from 2 mg to 4 mg, to reflect the appropriate dose allowed in the monograph for adults and children over 12 years of age (21 CFR 341). Since all pseudoephedrine-containing products were moved behind the counter, in compliance with The Combat Methamphetamine Epidemic Act of 2005, the proposed product is submitted in order to reestablish an OTC option for the consumer.

The original NDA had one pharmacokinetic study (AD-05-05) and no clinical efficacy and/or safety trial(s) were conducted in support of the application. In its review of the application, the Agency determined that the PK data for total PE (free + conjugated) was unreliable based on major flaws in the analytical assay methodology. The sponsor was requested to develop an adequately validated analytical assay method for quantifying unmetabolized (free) phenylephrine in plasma and use this method to either reanalyze plasma PK samples from study AD-05-05 or conduct an entirely new PK study and analyze plasma PE levels using the newly developed method. In addition, the original review also revealed that ibuprofen exhibits a delayed Tmax from the proposed combination product relative to historical values for ibuprofen alone. Therefore, the Agency requested that the sponsor address the potential impact of delayed ibuprofen Tmax on clinical efficacy in combination with PE and CHLOR.

1.4 Summary of Important Clinical Pharmacology Findings

In response, PCH conducted a new PK trial AD-08-10, using the final to-be-marketed formulation. This study investigated ibuprofen drug interaction, formulation effects and foods effects. A new and validated assay that measures free PE was employed in this study. This revised and revalidated assay specifically measures free PE in the sample as opposed to the total PE assay that was used in study AD-05-05 in the original submission. This new method was judged to be adequately validated to measure free PE in a previous review of Advil Congestion

Relief dated 01/14/2010 by Drs. Ying Fan and Atul Bhattaram under NDA 22-565 (ibuprofen and phenylephrine tablet; approved on 05/27/2010).

Study AD-08-10 characterized the rate and extent of IBU, PE and CHLOR absorption under fasted conditions from IBU/PE/CHLOR 200/10/4 mg caplets compared to marketed Motrin IB (IBU 200 mg), Sudafed PE (PE 10 mg) and Chlor-Trimeton (CHLOR 4 mg) single entity products administered concomitantly and to Motrin IB (IBU 200 mg) administered alone. Additionally, in the same study, the rate and extent of IBU, PE and CHLOR absorption from IBU/PE/CHLOR formulation was measured under fed condition to evaluate the food effect, if any (comparison of fasted vs. fed condition).

Relative Bioavailability under fasted state

Under fasted conditions, the IBU/PE/CHLOR caplet was equivalent in systemic exposure to the monoproducts administered together for all three ingredients of IBU, PE and CHLOR as 90% CIs around the ratios for AUCt, AUCinf and Cmax were all within the 80-125% limits for bioequivalence (Table 1).

Table 1. Mean (SD) PK parameters and Statistical Results for IBU, PE and CHLOR under fasted state.

| Treatments | AUCt (pg.hr/mL) | AUCinf (pg.hr/mL) | Cmax (pg/mL) |
|------------------------------|----------------------------|------------------------------|-------------------------|
| IBU | | | |
| IBU/PE/CHLOR combo | 67.1 (15.6) | 68.4 (15.6) | 17.7 (4.3) |
| IBU+PE+CHLOR monoproducts | 67.3 (16.1) | 68.4 (16.2) | 19.6 (4.7) |
| Combo/mono Ratio (90% CI) | 100.1 (97.5 - 102.7) | 100.3 (97.7 - 102.9) | 90.7 (85.2 - 96.6) |
| PE | | | |
| IBU/PE/CHLOR combo | 848.8 (274.9) | 892.5 (310.0) | 867.4 (456.2) |
| IBU+PE+CHLOR monoproducts | 803.8 (240.7) | 845.9 (249.9) | 992.6 (793.2) |
| Combo/mono Ratio (90% CI) | 104.6 (99.2-110.3) | 104.1 (98.4-110.2) | 90.4* (81.0-100.9)* |
| CHLOR | | | |
| IBU/PE/CHLOR combo | 145.8 (57.0) | 165.1 (76.1) | 6.7 (2.3) |
| IBU+PE+CHLOR monoproducts | 135.5 (52.0) | 153.2 (66.3) | 6.4 (2.0) |
| Combo/mono Ratio (90% CI) | 106.3 (102.9-109.8) | 105.8 (102.5-109.2) | 103.6 (98.3-109.3) |

* based on the statistical model excluding the IBU/PE/CHLOR fed treatment arm

Food Effect

No food effect was reported for CHLOR with respect to AUC and Cmax. While both IBU and PE was equivalent for AUC under fasted versus fed conditions, a food effect was observed for Cmax with IBU and PE. Under fed state, IBU and PE Cmax values decreased by 18% and 23%, respectively compared to fasted state (Table 2). In the first cycle of submission for the current NDA, study AD-05-05 reported a lack of food effect for IBU [ratio (90%CI) of 90.21 (81.72 - 99.58)]. In addition, Advil Congestion Relief also showed a similar observation of marginal food

effect for IBU [ratio (90% CI) of 87.6 (79.8 - 96.1)] which was attributed to the IBU component only and not to its co-administration with other active ingredients. Similar to this product, Advil Congestion Relief also showed a food effect of 22% decrease in Cmax for PE. Based on the observations above, a lack of clinically significant food effect can be concluded for all three active ingredients for the triple combination product of IBU/PE/CHLOR.

Table 2. Mean (SD) PK parameters and Statistical Results for IBU, PE and CHLOR under fasted vs. fed states.

| Treatments | AUCt (pg.hr/mL) | AUCinf (pg.hr/mL) | Cmax (pg/mL) |
|------------------------------|----------------------------|------------------------------|-----------------------------------|
| IBU | | | |
| IBU/PE/CHLOR - fasted | 67.1 (15.6) | 68.4 (15.6) | 17.7 (4.3) |
| IBU/PE/CHLOR - fed | 60.6 (13.9) | 62.1 (14.1) | 14.7 (4.3) |
| Fed/Fasted Ratio (90% CI) | 90.1 (87.8-92.5) | 90.6 (88.3-93.0) | 81.7 (76.7-87.0) |
| PE | | | |
| IBU/PE/CHLOR - fasted | 848.8 (274.9) | 892.5 (310.0) | 867.4 (456.2) |
| IBU/PE/CHLOR - fed | 817.0 (206.3) | 842.0 (207.3) | 650.1 (377.3) |
| Fed/Fasted Ratio (90% CI) | 97.8 (93.3-102.7) | 96.4 (91.6-101.3) | 77.3 (68.2-87.8) |
| CHLOR | | | |
| IBU/PE/CHLOR - fasted | 145.8 (57.0) | 165.1 (76.1) | 6.7 (2.3) |
| IBU/PE/CHLOR - fed | 141.7 (51.1) | 160.8 (73.8) | 6.8 (1.5) |
| Fed/Fasted Ratio (90% CI) | 99.4 (96.3-102.7) | 99.1 (96.0-102.3) | 105.0 (99.6-110.8) |

In the proposed label consistent with other IBU containing drug products, the patients are directed to take the drug product with food or milk if stomach upset occurs. This statement is supported by the conclusion of lack of significant food effect for all three active ingredients. The same language appears on Advil Congestion Relief label.

Delayed Tmax for IBU

As shown below in Table 3, under fasted state, the median IBU Tmax for the IBU/PE/CHLOR caplet was 15 minutes and 29.5 minutes longer than that for Motrin IB + Sudafed PE + Chlor-Trimeton (120 vs. 105 minutes) and Motrin IB tablets alone (120 vs. 90.5 min), respectively. This data is consistent with the previous findings from the original submission. Food had no effect on Tmax of the combination caplet (Table 3).

Table 3. Median Tmax of IBU after administration of IBU/PE/CHLOR combination caplet compared to that after administration of Motrin IB tablets.

| Treatments | Tmax (min) |
|-----------------------------------|-----------------------|
| IBU/PE/CHLOR - fasted | 120.0 |
| IBU/PE/CHLOR - fed | 120.0 |
| IBU+PE+CHLOR monoproducs - fasted | 105.0 |
| Motrin IB Tablets - fasted | 90.5 |

The sponsor provided Tmax values as well as efficacy data from previous NDAs associated with approved IBU containing drug products (Table 4). The data clearly demonstrated that products with longer Tmax (110-131 minutes) similar to the IBU/PE/CHLOR caplet (Tmax: 120 min) were significantly efficacious for the IBU component compared to placebo. These products were shown to provide acceptable onset of pain relief, fever reduction and onset of sleep. In addition, the infrequent use of rescue medication within the first two hours of taking these medications further indicates that subjects were receiving adequate pain relief. Some of these IBU-containing products also showed efficacy comparable to reference IBU-containing products with much shorter Tmax but comparable systemic exposure within their respective NDAs. These historical data, taken together, provided adequate evidence to conclude that prolongation of Tmax to 120 minutes would not have any significant impact on the IBU-dependent efficacy of the triple combination product of IBU/PE/CHLOR.

Table 4. Summary of clinical data from previous NDAs of approved IBU containing drug products with comparable Tmax to IBU/PE/CHLOR caplet

| NDA # | Product | Ingredients | Tmax (min) | Clinical Data |
|--------|-------------------------|----------------------------------|------------|---|
| 21-441 | Advil Allergy Sinus | IBU/PSE/CHLOR (200/30/2 mg) | 110 | Significant analgesia with 1 caplet at 2 and 3 hrs post first dose in allergy sufferers with moderate to severe allergy-associated pain. |
| 20-944 | Advil Chew Tabs | IBU (100 mg) | 112 | Comparable efficacy (reduction of sum of temperature differences over 2, 4 and 6 hours and onset of temperature control) between Advil Chew and Advil suspension (Tmax: 39 min) in febrile 2-11y. |
| 20-135 | Motrin Chew Tabs | IBU (50 mg) | 117 | Comparable efficacy (temperature reductions through 5 hrs) between Motrin Chew and IBU suspension (Tmax: 41 min) in febrile 2-11y. |
| 21-394 | Advil PM Caplet | IBU/DPH* (200/38 mg) (200/25 mg) | 131 | Efficacy** (objective total sleep time, sleep latency, median time to remedication over the first 3 hrs) demonstrated over placebo in subjects with pain associated with sleeplessness. |
| 22-565 | Advil Congestion Relief | IBU/PE (100/10 mg) | 120 | None |

* DPH = Diphenhydramine. The difference in DPH weight in the two products (38 mg vs. 25 mg) is a result of its being formulated as either a citrate salt or hydrochloride salt in the caplet and liquigel, respectively.

** sleep latency and remedication rate over the first 3 hours is attributed to the IBU component

In addition to above, the sponsor also developed a PK/PD model for IBU in dental pain that could characterize PK profiles of different formulations, establish IBU exposure-response relationships for pain relief or remedication, and create PK nomograms to evaluate the effect of IBU formulations on time to meaningful pain relief (TMPR) and time to first perceptible pain relief (TFPR) and time to remedication (REMD) to support the efficacy of IBU containing drug products with prolonged Tmax values. The same model had been submitted to support Advil Congestion Relief. Simulations were conducted to evaluate the impact of 30 minute delay (1.5 hr vs. 2 hr) in Tmax between single-ingredient IBU product and the double combination (IBU/PE) on pain relief. It was concluded that 30 minute difference in median Tmax, which is also the case in this application, did not appear to translate into major differences in pain relief score.

Drug-Drug Interaction

Lack of clinically relevant drug-drug interactions between these three active components are addressed by the following taken together: 1) lack of interaction between CHLOR and PE per OTC Cold and Cough monograph for Over-The-Counter Human Use (21 CFR 341), 2) lack of

interaction between IBU and CHLOR per approval of Advil Allergy Sinus Caplets (triple combination of ibuprofen, pseudoephedrine and chlorpheniramine), and 3) lack of interaction between IBU and PE per approval of Advil Congestion Relief (double combination of ibuprofen and phenylephrine). For additional details, refer to section 2.5.2 under Question Based Review.

2 QUESTION BASED REVIEW

2.1 General Attributes

Refer to Clinical Pharmacology review of original submission by Dr. Partha Roy dated 06/06/2008 for general attributes and proposed mechanism of action, indication, dosage and route of administration.

2.2 General Clinical Pharmacology

2.2.1 What clinical studies were conducted to support this NDA?

This is a 505 (b) (2) application based on PK program only. No clinical efficacy and safety trial was conducted. Initially, clinical pharmacology study AD-05-05 was submitted in the original NDA 22-113. 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. In response, PCH conducted a new PK study AD-08-10, using the final to-be-marketed formulation. This study investigated ibuprofen drug interaction, formulation effects and foods effects.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

IBU (racemate) and CHLOR were appropriately measured in human plasma. Please refer to Section 2.6 Analysis for analytical details.

For PE, a new and validated assay that measures free PE was employed in this study. This revised and revalidated assay specifically measures free PE in the sample as opposed to the total PE (free PE + conjugated PE) assay that was used previously in study AD-05-05.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response?

Refer to Clinical Pharmacology review of original submission by Dr. Partha Roy dated 06/06/2008 for gender effects on IBU and CHLOR pharmacokinetics.

2.4 Extrinsic Factors

Not applicable

2.5 General Biopharmaceutics

2.5.1 Is there a formulation effect for the proposed combination drug product?

There is no formulation effect on the pharmacokinetics of the three drug components as a result of combining these three ingredients in a new triple combination immediate-release drug product. Under fasted conditions, the IBU/PE/CHLOR caplet was equivalent in systemic exposure to the monoproducts administered together for all three ingredients of IBU, PE and CHLOR as 90% CIs around the ratios for AUC_t, AUC_{inf} and C_{max} were all within the 80-125% limits for bioequivalence (Table 1).

2.5.2 Is there a potential for drug-drug interaction between CHLOR and PE, IBU and PE, and IBU and CHLOR?

The triple combination of an analgesic, decongestant, and antihistamine and double combinations of antihistamine / decongestant and antihistamine / analgesic are all considered Category I combinations, i.e. permitted combinations as per the OTC monograph (21CFR 341.40). There are many three-ingredient combination products containing an analgesic / decongestant / antihistamine currently marketed OTC, including the triple combination of IBU/PSE/CHLOR that the company seeks to replace with a new triple combination containing PE as the decongestant of choice instead of pseudoephedrine (PSE).

One of the key findings from the triple combination is that IBU exhibits delayed T_{max} in combination compared to IBU monoproduct as shown in study AD-08-10 (median T_{max} of 120 hrs vs. 90.5 hrs as listed in Table 3). This trend was also noted in study AD-05-05 submitted with the original submission where the mean T_{max} from the combination was found to be 2.17 hrs, determined to be about 1 hour delayed compared to historical values for ibuprofen alone (refer to Dr. Partha Roy's Clinical Pharmacology Review dated 06/06/2008). The sponsor was asked in the Not Approval letter to address the potential impact of delayed IBU T_{max} on clinical efficacy in combination with PE and CHLOR. In response, the sponsor included a Motrin IB alone treatment arm in the pivotal study AD-08-10 to compare T_{max} values between the combination and the IBU individual product (Motrin IB).

As shown earlier in Table 3, under fasted state, the median IBU T_{max} for the IBU/PE/CHLOR caplet was 15 minutes and 29.5 minutes longer than that for the treatments arms Motrin IB, Sudafed PE and Chlor-Trimeton administered together and Motrin IB tablets administered alone, respectively. Food had no effect on T_{max} of the combination caplet.

In order to address the clinical significance of prolonged T_{max} from the combination, the sponsor provided T_{max} values as well as efficacy data from previous NDAs associated with approved IBU containing drug products (Table 4). The data clearly demonstrated that products with longer T_{max} (110-131 minutes) similar to the IBU/PE/CHLOR caplet from this NDA (T_{max}: 120 min) were found to be efficacious for the IBU component compared to placebo. Specifically, these products were shown to provide acceptable onset of pain relief, fever reduction and onset of sleep. In addition, the infrequent use of rescue medication within the first two hours of taking these medications further indicates that subjects were receiving adequate pain relief. These IBU-containing products also showed efficacy comparable to reference IBU-containing products with much shorter T_{max} but comparable systemic exposure within their

respective NDAs. These historical data, taken together, provided adequate evidence to conclude that prolongation of Tmax to 120 minutes would not have significant impact on the IBU-dependent efficacy of the triple combination product of IBU/PE/CHLOR.

In addition to above, the sponsor also developed a PK/PD model for IBU in dental pain that could characterize PK profiles of different formulations, establish IBU exposure-response relationships for pain relief or remedication, and create PK nomograms to evaluate the effect of IBU formulations on time to meaningful pain relief (TMPR) and time to first perceptible pain relief (TFPR) and time to remedication (REMD) to support the efficacy of IBU containing drug products with prolonged Tmax values. The same model had been submitted to support the recently approved double combination product (IBU/PE 100/10 mg) and has been reviewed under NDA 22-565 (refer to the Clinical Pharmacology review by Drs. Ying Fan and Atul Bhattaram dated 1/14/2010). Simulations were conducted to evaluate the impact of 30 minute delay (1.5 hr vs. 2 hr) in Tmax between single-ingredient IBU product and the double combination (IBU/PE) product on pain relief. It was concluded that 30 minute difference in median Tmax, which is also the case in this application, did not appear to translate into major differences in pain relief score. Based on the PK nomograms of TFPR and TMPR following oral administration of IBU in the patients, the sponsor concluded that the difference in TFPR between Motrin IB (median Tmax: 90.5 min) and IBU/PE/CHLOR (median Tmax: 120 min) in study AD-08-10 is likely to be less than 6 minutes. Based on all the above, the sponsor adequately addressed the issue of delayed Tmax and provided sufficient clarity to understand the likely impact of delayed Tmax of IBU in combination with CHLOR and PE on clinical efficacy.

Separate from the issue of delayed IBU Tmax, drug-drug interaction potential between the three ingredients of IBU, CHLOR and PE is being addressed in this application with adequate support from OTC regulations and previous approvals. Lack of clinically relevant drug-drug interactions between these three active components are concluded by the following:

1. The combination of CHLOR and PE is provided for in the OTC Cold and Cough monograph for Over-The-Counter Human Use (21 CFR 341).
2. Lack of drug-drug interaction between IBU and CHLOR was previously concluded by the Agency. Refer to Clinical Pharmacology review of NDA 21-441 for Advil Allergy Sinus Caplets (triple combination of ibuprofen, pseudoephedrine and chlorpheniramine) by Dr. Tapash Ghosh dated 08/08/2002 for details.
3. Lack of drug-drug interaction between IBU and PE was previously concluded by the Agency. Refer to Clinical Pharmacology review of NDA 22-565 for Advil Congestion Relief (double combination of ibuprofen and phenylephrine) by Drs. Ying Fan and Atul Bhattaram dated 01/14/2010 for details.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

No food effect was reported for CHLOR with respect to AUC and Cmax. While both IBU and PE met the equivalence criteria (90% confidence interval around the ratio of means) for AUC under fasted versus fed conditions, a food effect was observed for Cmax with IBU and PE. Under fed state, IBU and PE Cmax decreased by approximately 18% and 23%, respectively compared to fasted state (Table 5). In contrast, study AD-05-05 results submitted with the original submission of the current NDA, reported a lack of food effect for IBU [ratio (90%CI) of

90.21 (81.72 - 99.58)]. However, Advil Congestion Relief also exhibited similar magnitude with 90% CI around the ratio of the means just outside the equivalence criterion of 80-125% for IBU [ratio (90% CI) of 87.6 (79.8 - 96.1)], indicating a slight food effect. This was attributed to the IBU component only and not to its co-administration with other active ingredients. Advil Congestion Relief also showed a food effect of 22% decrease in C_{max} for PE, which was similar to the food effect data for PE in this product. Taken together the observations discussed above, a lack of clinically significant food effect can be concluded for all three active ingredients for the triple combination caplet of IBU/PE/CHLOR.

Table 5. Mean (SD) C_{max} and statistical results (ratio and 90% CI) of IBU and PE under fasted vs. fed states.

| Treatments | C_{max} (pg/mL) |
|------------------------------|------------------------------------|
| IBU | |
| IBU/PE/CHLOR - fasted | 17.7 (4.3) |
| IBU/PE/CHLOR - fed | 14.7 (4.3) |
| Fed/Fasted Ratio (90% CI) | 81.7 (76.7-87.0) |
| PE | |
| IBU/PE/CHLOR - fasted | 867.4 (456.2) |
| IBU/PE/CHLOR - fed | 650.1 (377.3) |
| Fed/Fasted Ratio (90% CI) | 77.3 (68.2-87.8) |

In the proposed label consistent with other IBU containing drug products, the patients are directed to take the drug product with food or milk if stomach upset occurs. This statement is supported by the conclusion of lack of significant food effect for all three active ingredients. The same language also appears on the recently approved Advil Congestion Relief label.

2.6 Analytical Section

2.6.1 Were the analytical methods used to determine IBU, CHLOR and PE in plasma adequately validated?

Plasma samples were analyzed for IBU, PE and CHLOR using validated methods of liquid chromatography with tandem mass spectrometry (LC/MS/MS):

1. IBU using HPLC with MS/MS.
2. Unconjugated (free) PE using HPLC with MS/MS.
3. CHLOR using HPLC with MS/MS.

IBU

A 100- μ L sample aliquot is fortified with 25 μ L of 25 μ g/mL internal standard working solution and diluted with 100 μ L of 0.1 M phosphoric acid. Analytes are isolated by a liquid/liquid

extraction using 90:10 hexane/isopropyl alcohol, v/v. 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.

PE

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 solid phase extraction using Phenomenex strata-X-CW, 10-mg, 33- μm , 96-well SPE 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 300 μL of 2% formic acid in acetonitrile by centrifugation. The eluate is directly injected and analyzed via HPLC with MS/MS detection.

CHLOR

A 50 μL sample aliquot is transferred to a conical-bottom, 96-well plate and fortified with 25 μL of internal standard working solution. A 350 μL volume of acetonitrile is added to the plate to precipitate protein; then the plate is shaken and centrifuged. A 50 μL supernatant solution is then transferred to a new conical-bottom, 96-well plate and diluted with 400 μL of 0.1% formic acid solution. A 30- μL of the final extract is injected and analyzed via HPLC with MS/MS detection.

Accuracy and precision was determined as part of method validation. Intra- and inter-assay accuracy was assessed in terms of the mean error of the replicate set expressed as the percent deviation from the theoretical concentration. Intra- and inter-assay precision was assessed in terms of the relative standard deviation of the measured concentration expressed as the percent coefficient of variation. The results for these assessments are presented in Table 6.

Table 6. Assessment of accuracy and precision of assay methodologies for IBU, PE and CHLOR.

| | Analyte (Assay Method No.) | | |
|-----------------------------|-----------------------------------|--------------------------------|-----------------------------|
| | IBU (LCMS B409) | PE (LCMSC 392.1 v2) | CHLOR (LCMS 214) |
| 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 | 0.200 mcg/mL | 10 pg/mL | 0.25 ng/mL |

Office of Clinical Pharmacology (OCP) requested a NDA pre-approval data validation inspection of the study AD-08-10 to the OSI. The audit report from OSI is still pending at the time of completion of this review.

3 Labeling Recommendation:

There are no labeling comments or edits from the clinical pharmacology perspective. The label does not contain any relevant clinical pharmacology information. Refer to the appropriate reviews from ONP/DNCE for details of labeling review comments.

4 Appendix

4.1 Individual Study Review (AD-08-10)

Title: A Four-Way Crossover, Bioavailability Study Of A Caplet Formulation Containing Ibuprofen 200 Mg, Phenylephrine Hydrochloride 10 Mg And Chlorpheniramine Maleate 4 Mg

Objectives:

1. To characterize under fasted conditions, the rate and extent of absorption of IBU, PE and CHLOR from a triple combination caplet containing IBU/PE/CHLOR 200/10/4 mg compared to single ingredient products of Motrin IB (IBU 200 mg), Sudafed PE (PE 10 mg) and Chlor-Trimeton Allergy (CHLOR 4 mg) administered together;
2. To evaluate the food-effect of IBU, PE and CHLOR from the triple combination caplet containing IBU/PE/CHLOR 200/10/4 mg.
3. To characterize, under fasted conditions, the rate and extent of absorption of IBU from a caplet containing IBU/PE/CHLOR 200/10/4 mg compared to Motrin IB (IBU 200 mg) administered alone.

Subjects:

Fifty-six (56) healthy male and female subjects between 18-45 years of age with body mass index 18-29 kg/m² and body weight of at least 50 kg were to be enrolled to ensure that approximately 48 subjects would complete the study. Fifty six healthy were enrolled and all subjects completed the study.

Design:

This is a randomized, open-label, cross-over, single dose bioavailability study with each subject receiving the following treatments with a washout interval of 7 days:

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

PK Results:

The mean plasma IBU, PE and CHLOR concentration-time plots are presented in Figure 1, Figure 2 and Figure 3, respectively. The PK summary results of IBU, PE and CHLOR for the different comparisons with the primary analysis population are summarized in Table 1, Table 2 and Table 3, respectively. Under fasted conditions, the IBU/PE/CHLOR caplet demonstrated equivalent exposure (AUC and C_{max}) to single ingredient IBU, PE and CHLOR administered concomitantly for IBU and CHLOR. The lower bound of the 90% confidence intervals for PE fell just outside on C_{max} (79.7-102.5) when data from all treatments was analyzed together. The

intrasubject CV% dropped from 42% to 36% and 90% confidence intervals fell within the limits (81.0-100.9), when data from fasted treatments only (relevant treatments for establishing BE) was analyzed, thereby concluding equivalence on C_{max} for PE. The IBU/PE/CHLOR caplet also exhibited equivalent systemic exposure to IBU alone for both AUC and C_{max}. Under fed versus fasted conditions, the IBU/PE/CHLOR caplet was equivalent (AUC and C_{max}) to CHLOR, indicating lack of food effect. A significant food effect was observed for C_{max} with both IBU and PE.

Table 1. IBU PK parameters - Mean (SD) [Median], Ratios and 90% CIs

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

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

Note: Median is presented to T_{max} only.

Table 2. PE PK parameters - Mean (SD) [Median], Ratios and 90% CIs

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

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

Note: Median is presented to T_{max} only.

Table 3. CHLOR PK parameters - Mean (SD) [Median], Ratios and 90% CIs

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

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

Note: Median is presented to T_{max} only.

**Figure 1: AD-08-10 Mean Plasma Ibuprofen Concentrations over Time
(Linear, through 8 hours)**

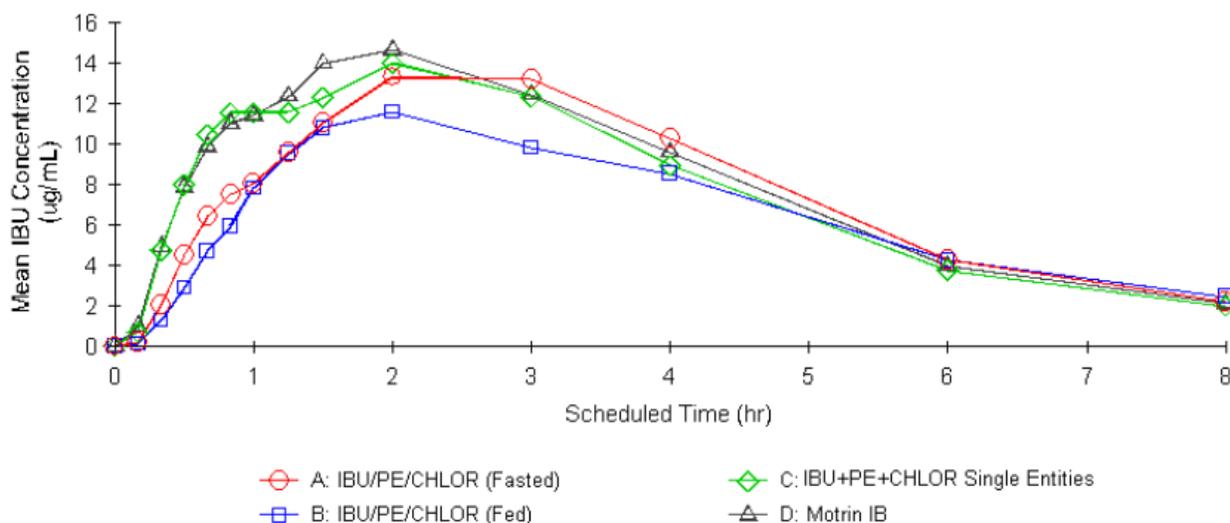


Figure 2: AD-08-10 Mean Plasma Phenylephrine Concentrations over Time (Linear, through 8 hours)

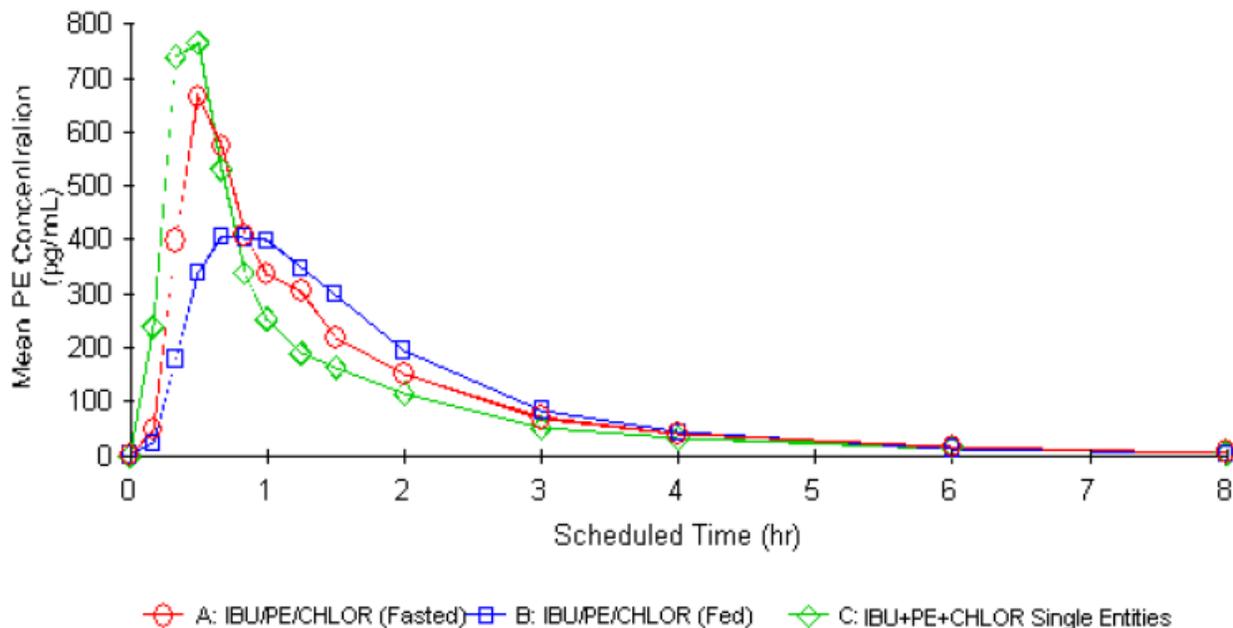
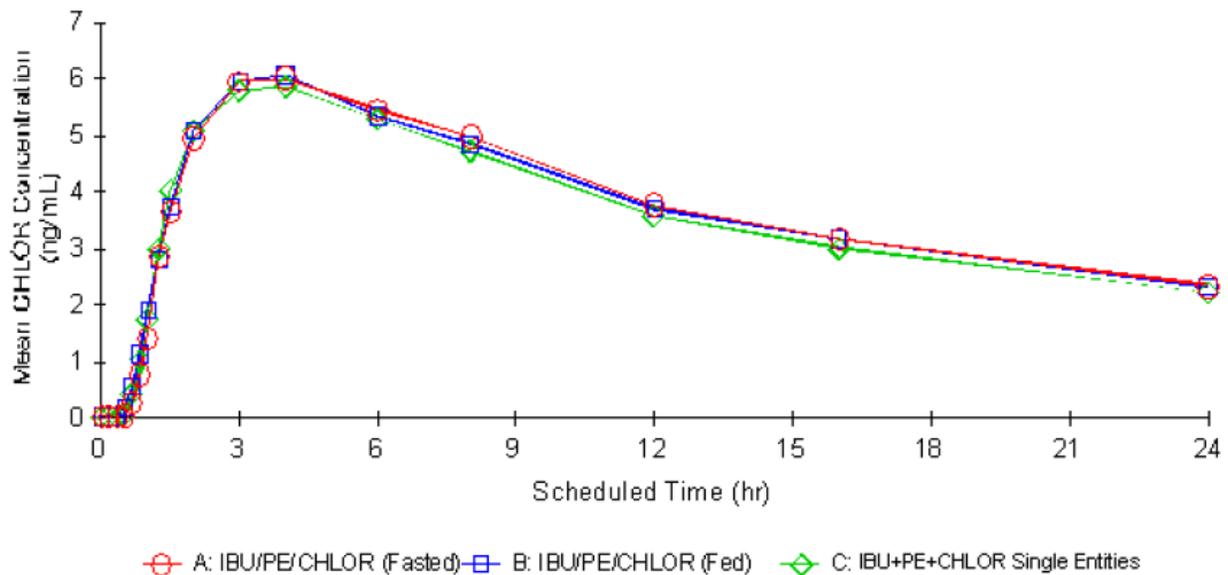


Figure 3: AD-08-10 Mean Chlorpheniramine Concentrations over Time (Linear, through 24 hours)



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/s/

PARTHA ROY
11/16/2011

SURESH DODDAPANENI
11/16/2011

CLINICAL PHARMACOLOGY REVIEW

| | |
|----------------------------------|--|
| NDA 22-113: | Submission Date: September 25, 2007 |
| Generic Name: | Ibuprofen / Phenylephrine / Chlorpheniramine |
| Brand Name: | (b) (4) |
| Reviewers: | Partha Roy, Ph.D. |
| Team Leader (Acting): | Wei Qiu, Ph.D. |
| OCP Division: | Clinical Pharmacology 2 (DCP2) |
| OND Division: | DNCE/ONP |
| Sponsor: | Wyeth Consumer Healthcare (WCH) |
| Submission Type: | Original |
| Formulation; Strength(s): | Caplets; Ibuprofen 200 mg / Phenylephrine HCl 10 mg / Chlorpheniramine Maleate 4 mg |
| Indications: | Temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor body aches and pains, fever. |

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1 EXECUTIVE SUMMARY

This is a 505 (b)(2) NDA application for a new triple combination of ibuprofen (IBU) (200 mg), phenylephrine (PE) (10 mg) and chlorpheniramine (CHLOR)(4 mg) to provide an alternative to the ibuprofen (200 mg)/pseudoephedrine HCl (30 mg)/chlorpheniramine (2 mg) product currently marketed under the trade name Advil Allergy Sinus caplets (NDA 21-441) as a combination pain reliever/fever reducer, nasal decongestant and antihistamine for age 12 years and above. Since all pseudoephedrine-containing products were moved behind the counter, in compliance with The Combat Methamphetamine Epidemic Act of 2005, the proposed product is submitted in order to reestablish an OTC option for the consumer. It is noted that the dose of CHLOR maleate has been adjusted from 2 mg to 4 mg, to reflect the appropriate dose allowed in the monograph for adults and children over 12 years of age (21 CFR 341). The Sponsor requested a pediatric study waiver for age 12 years and below. PREA is triggered by this NDA; if approved, the sponsor will be required to develop age-appropriate formulations down to 2 years of age as per Cross-Discipline Team Leader Review by Dr. Bindi Nikhar (dated 6/2/2008).

No clinical efficacy and safety trial was conducted. A total of one human pharmacokinetic study has been submitted in support of this NDA. Study AD-05-05 is a single-dose, three-way crossover, food/formulation effect bioavailability study with an earlier development formulation of IBU/PE/CHLOR. Following the completion of Study AD-05-05, the final to-be-marketed formulation was changed to include an antioxidant preservative (b)(4) propyl gallate or "PG") (b)(4). The Sponsor proposed to use comparative *in vitro* dissolution data in support of a waiver of *in vivo* bioequivalence study between the non-PG (clinical) and PG (commercial) formulations. The approach was discussed at the Pre-NDA meeting (March 19, 2007) and found acceptable by the Agency. At the time of this review, the comparative *in vitro* dissolution data is being reviewed by the CMC reviewer. (*Reviewer's Note: Meanwhile, the sponsor conducted a bridging bioequivalence study (AD-06-06) between the two formulations but did not submit the data in this NDA.*)

A site inspection was conducted by the Division of Scientific Investigations (DSI) for the clinical and analytical portions of the pivotal PK study, AD-05-05. Major flaws were identified for the analytical assay that quantifies the total PE (unmetabolized PE plus PE converted back from conjugated PE metabolites). The assay method problems include incomplete hydrolysis of conjugated PE metabolites, PE instability in the hydrolysis buffer, and lack of appropriate quality controls. Refer to DSI reviewer's memo (Appendix 4.3) for details. Based on the findings of DSI inspection of this study, it is our opinion that the PE data contained in Study AD-05-05 can no longer be considered acceptable based on the regulatory standards to support this NDA.

1.1 Recommendations

From a Clinical Pharmacology perspective, NDA 22-113 is not acceptable because the PK data for PE in the NDA submission were not reliable due to major flaws with the bioanalytical method at the (b)(4) analytical site identified by DSI. The sponsor has two options to resolve the PE analysis issues: 1) reanalyze the stored PK samples from study AD-05-05 using an adequately

validated analytical method for PE or 2) conduct an entirely new PK study identical in design to study AD-05-05 with the to-be-marketed caplet formulation of IBU/PE/CHLOR and analyze the newly acquired PK samples using an adequately validated analytical method for PE.

The following deficiency should be conveyed to the Sponsor as appropriate:

In view of the analytical assay methodology issues and the unreliability of the submitted plasma PE concentration data in this NDA submission, the PK data for PE to support this NDA is deemed not acceptable. To resolve the PE assay issue, you are recommended to develop an adequately validated sensitive assay for quantifying unmetabolized (free) PE in human plasma. You will need to either 1) reanalyze the stored PK samples from study AD-05-05 provided stability of these samples can be assured or 2) repeat the pivotal BE study with the to-be-marketed formulation of IBU/PE/CHLOR and analyze the newly acquired PE PK samples, using the validated analytical method for free PE.

In addition, the following comment should be conveyed to the Sponsor as appropriate:

Cross-study comparison of ibuprofen PK data from your proposed triple combination caplet (Study AD-05-05) to the historical ibuprofen PK data suggested that the mean T_{max} values of ibuprofen increased approximately 1 hr in the presence of phenylephrine and chlorpheniramine. Therefore, you need to address the potential impact of delayed T_{max} of IBU from your proposed product on clinical efficacy.

1.2 Phase 4 Commitments

Not Applicable.

1.3 Summary of Important Clinical Pharmacology Findings

This application is supported by one pharmacokinetic study (AD-05-05). Study AD-05-05 evaluated the formulation effect by assessing bioequivalence of the test product with that of IBU 200 mg (Motrin® IB tablet), PE 10 mg (Sudafed® PE caplet) and CHLOR 4 mg (Chlor-Trimeton® Allergy tablet) single entity products administered concomitantly. Food effect was also evaluated in this study in the presence of FDA-standardized high-fat, high-calorie meal.

Because of analytical issues with PE, data for IBU and CHLOR are discussed only.

The PK data suggested no formulation effect for IBU and CHLOR as 90% confidence intervals of the caplet/single entity ratio for all key PK parameters fell within the 80-125% limits for bioequivalence (Tables 1-2).

No food effect was detected for both IBU and CHLOR where the 90% confidence intervals around the ratios of AUCL, AUCI and C_{max} for the comparison of IBU/PE/CHLOR caplet under fed vs. fasted states were all within the 80-125% bioequivalence limits (Tables 1-2). Mean T_{max} values for IBU and CHLOR between fed and fasted states were generally comparable.

Table 1. Formulation/Food Effect: Mean (SD) IBU Pharmacokinetic Parameters and Statistical Analysis (N = 40) (Study AQ-05-05).

| | AUCL (mcg•h/mL) | AUCI [#] (mcg•h/mL) | C _{max} (mcg/mL) | T _{max} (h) | T _{1/2} [#] (h) |
|--|--------------------------|---------------------------------|------------------------------|-------------------------|--------------------------------------|
| Mean (SD) | | | | | |
| Treatment A | 73.01 (14.16) | 74.19 (14.16) | 20.40 (4.29) | 2.17 (1.05) | 2.15 (0.47) |
| Treatment B | 65.70 (14.58) | 67.26 (14.65) | 19.27 (6.76) | 1.91 (1.41) | 2.22 (0.39) |
| Treatment C | 73.31 (18.37) | 74.60 (18.22) | 22.08 (5.93) | 1.80 (0.94) | 2.15 (0.59) |
| Geometric Mean Ratio (%) (90% Confidence Intervals)[^] | | | | | |
| B(fed) / A(fasted)*% | 89.64 (85.14-94.38) | 89.61 (85.24-94.21) | 90.21 (81.72-99.58) | — | — |
| A(combination) / C(concomitant)* % | 101.19 (96.11-106.54) | 100.86 (95.99-105.98) | 94.79 (85.86-104.65) | — | — |

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

n = 39 (terminal phase not accurately calculated for subject 108, hence no included)

Treatment A: IBU/PE/CHLOR Caplet – Fasted

Treatment B: IBU/PE/CHLOR Caplet – Fed

Treatment C: Motrin IB Tablet + Sudafed PE Caplet + Chlor-Trimeton Allergy tablet (administered together) - Fasted

Table 2. Formulation/Food Effect: Mean (SD) CHLOR Pharmacokinetic Parameters (N = 40) (Study AQ-05-05).

| | AUCL (mcg•h/mL) | AUCI (mcg•h/mL) | C _{max} (mcg/mL) | T _{max} (h) | T _{1/2} (h) |
|--|--------------------------|--------------------------|------------------------------|-------------------------|-------------------------|
| Mean (SD) | | | | | |
| Treatment A | 149.54 (51.73) | 169.50 (68.97) | 7.11 (1.61) | 4.03 (1.25) | 19.35 (8.40) |
| Treatment B | 151.72 (52.86) | 171.80 (66.28) | 7.21 (1.55) | 3.73 (1.57) | 19.81 (7.28) |
| Treatment C | 158.03 (51.60) | 175.33 (62.47) | 7.47 (1.66) | 3.86 (1.38) | 18.79 (5.70) |
| Geometric Mean Ratio (%) (90% Confidence Intervals)[^] | | | | | |
| B (fed)/A (fasted)* % | 101.40 (98.07-104.83) | 101.93 (98.27-105.72) | 101.80 (98.46-105.26) | — | — |
| A (combination caplet) /C (single ingredients together)* % | 93.81 (90.73-96.99) | 94.98 (91.57-98.52) | 95.18 (92.05-98.41) | — | — |

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

Treatment A: IBU/PE/CHLOR Caplet – Fasted

Treatment B: IBU/PE/CHLOR Caplet – Fed

Treatment C: Motrin IB Tablet + Sudafed PE Caplet + Chlor-Trimeton Allergy tablet (administered together) - Fasted

(b) (4)

compared to historical single ingredient IBU PK data, PE appeared to delay T_{max} of IBU by ~0.6 hour in males (Table 3). Adding CHLOR to IBU and PE seems to further delay T_{max} of IBU resulting in a significant delay of 1 hour between the triple combination caplet and historical Nuprin® data (Table 3). Mean AUC and C_{max} values were comparable between IBU alone, IBU/PE and IBU/PE/CHLOR caplets.

Table 3. Cross-Study Comparison of IBU PK: Study AQ-05-03 IBU/PE (fasted), Study AD-05-05 IBU/PE/CHLOR (fasted) vs. Historical IBU Data (male subjects only).

| | AUCI ($\mu\text{g}\cdot\text{h}/\text{mL}$) | Cmax ($\mu\text{g}/\text{mL}$) | Tmax (h) |
|--|---|--|---------------------|
| Means | | | |
| AQ-05-03 IBU/PE- fasted* | 66.92 | 18.49 | 1.86 |
| AD-05-05 IBU/PE/CHLOR- fasted* | 72.33 | 19.78 | 2.25 |
| IBU Historical data for Nuprin 200 mg tablets-fasted** | 64.94 | 20.25 | 1.26 |
| Ratio% | Difference | | |
| AQ-05-03 / Historical data | 103.05 | 91.31 | 0.6*** |
| AD-05-05 / Historical data | 111.38 | 97.68 | 1.0*** |

* From the summary of IBU PK parameters from IBU/PE (study AQ-05-03) and IBU/PE/CHLOR Caplet (AD-05-05) -Fasted for males (n=19).

** From the weighted (by sample size) average of PK values of AUCI, Cmax and Tmax from eight studies which included Nuprin 200 mg tablets based on males only (see Appendix 4.2.2 individual study review).

*** Difference in means

Because no clinical trial was conducted with this new combination product of IBU/PE/CHLOR, IBU PK/PD models for both analgesic (dental pain) and antipyretic (febrile fever) was used to help understand the likely clinical effect of delayed Tmax of IBU for this combination product

(b) (4)

We determined percentage of subjects who had plasma IBU levels above 6 and 10 $\mu\text{g}/\text{mL}$ (EC50 range for dental pain and febrile fever) at 30 and 60 minutes following administration of the proposed combination caplet under fasted state to assess likely clinical effect of delayed Tmax of IBU.

Delayed IBU Tmax in IBU/PE/CHLOR combination product compared to IBU single ingredient product (Nuprin®) led to ~50% lower percentage of subjects reaching EC50 at early time points (≤ 1 hr). As shown in Table 4, 27% and 42% study subjects had IBU plasma concentrations ≥ 10 $\mu\text{g}/\text{mL}$ at 30 min and 60 min, respectively, following single-dose administration of the combination caplet. In comparison, 55% and 86% of the subjects had IBU plasma concentrations ≥ 10 $\mu\text{g}/\text{mL}$ at 30 min and 60 min, respectively as evident from the historical IBU PK data from IBU single ingredient Nuprin®. Similar trend was also evident when 6 $\mu\text{g}/\text{mL}$ was set to be the EC50 benchmark for comparison (Table 4). Depending on the importance of onset of analgesic/antipyretic for the proposed indication, the delayed Tmax of IBU for the IBU/PE/CHLOR combination caplet may be clinically undesirable.

Table 4. Cross-study comparisons of IBU plasma concentrations at 30 min and 60 min in subjects receiving IBU/PE/CHLOR caplet (NDA 22-113) and Nuprin® (IBU alone from NDA 20-135: historical data) under fasted state.

| | NDA 22-113 (this submission) | | NDA 20-135 (historical) | |
|--|------------------------------|---------------|-------------------------|---------------|
| | 30 min | 60 min | 30 min | 60 min |
| % of Subjects $\geq 6 \mu\text{g/mL}$ | 45 (18/40) | 70 (28/40) | 77 (17/22) | 92 (22/24) |
| % of Subjects $\geq 10 \mu\text{g/mL}$ | 27 (11/40) | 42 (17/40) | 55 (12/22) | 86 (19/24) |
| Mean ($\mu\text{g/mL}$) | 7.3 | 10.1 | 13.8 | 16.3 |
| SD ($\mu\text{g/mL}$) | 5.2 | 6.9 | 9.7 | 6.7 |
| CV% | 71.8 | 68.0 | 33.8 | 29.0 |

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Table 2.1.1.1. Physical-chemical Properties of IBU.

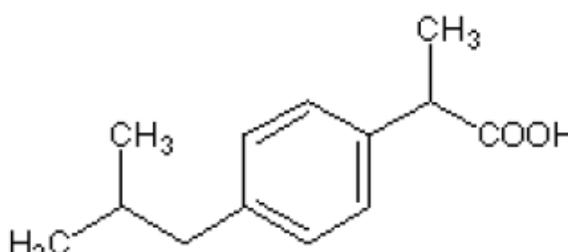
| | |
|-------------------|---|
| Drug Name | Ibuprofen |
| Chemical Name | (±)-2-(<i>p</i> -Isobutylphenyl)propionic acid |
| Structure |  |
| Molecular Formula | C ₁₃ H ₁₈ O ₂ |
| Molecular Weight | 206.28 |
| Melting Point | 75 - 78°C |
| Appearance | White or almost white powder or crystals with a characteristic odor |
| Solubility | Practically insoluble in water; 1 part ibuprofen soluble in 1.5 (w/w) parts of alcohol, 1 part chloroform, 2 parts ether, or 1.5 parts acetone; Also soluble in an aqueous solution of alkali hydroxides and carbonates |

Table 2.1.1.2. Physical-chemical Properties of PE.

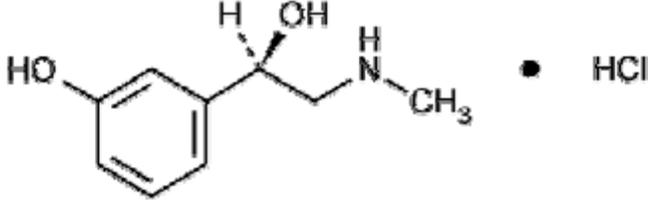
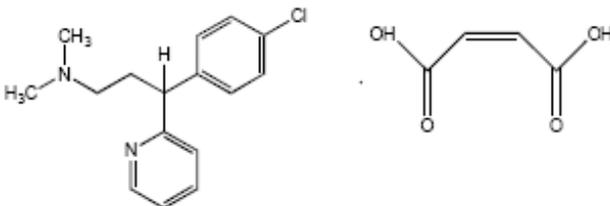
| | |
|-------------------|---|
| Drug Name | Phenylephrine Hydrochloride |
| Chemical Name | (-)- <i>m</i> -Hydroxy- α -[(methylamino)methyl]benzyl alcohol hydrochloride |
| Structure |  |
| Molecular Formula | C ₉ H ₁₃ NO ₂ •HCl |
| Molecular Weight | 203.67 |
| Melting Point | 140-145°C. |
| Solubility | Very soluble in water and alcohol and practically insoluble in ether |

Table 2.1.1.3. Physical-chemical Properties of CHLOR.

| | |
|-------------------|--|
| Drug Name | Chlorpheniramine Maleate |
| USP Chemical Name | 2-[<i>p</i> -Chloro- α -[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) |
| Structure |  |
| Molecular Formula | C ₁₆ H ₁₉ ClN ₂ •C ₄ H ₄ O ₄ |
| Molecular Weight | 390.86 |
| Melting Point | 130 - 135°C |
| Appearance | White or almost white powder or crystals with no odor |
| Solubility | 330 mg/mL in ethanol, 240 mg/mL in chloroform, 160 mg/mL in water and 13 mg/mL in methanol at 25°C. Slightly soluble in benzene and ether. |

The quantitative composition of (b) (4) is shown in Table 2.1.1.4. Each caplet contains 200 mg of IBU, 10.0 mg of PE hydrochloride, and 4.00 mg of CHLOR maleate with an additional 281 mg of inactive ingredients to have a total caplet weight of 495 mg. The product is packaged in an Aclar UltRx 2000 white opaque child-resistant blister and one-count pouches.

Table 2.1.1.4. Quantitative Composition of (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 Colloidal NF (b) (4) | 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 | | | |

Table 2.1.1.4. Quantitative Composition of

(b) (4)

(Continued)

(b) (4)



processing.

2.1.2 What is the proposed dosage and route of administration?

The caplets are to be taken orally. Following directions are proposed as per label:

- do not take more than directed.
- do not take longer than (b) (4) days, unless directed by a doctor.
- adults and children 12 years of age and over.
- 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.
- children under 12 years of age: do not use.

2.1.3 What is the proposed mechanism of drug action and therapeutic indications?

IBU is a non-steroidal anti-inflammatory drug (NSAID). Like all NSAIDs, it has analgesic, antipyretic, and anti-inflammatory properties. The mechanism of action of NSAIDs is attributed to reduction of prostaglandin biosynthesis via non-selective inhibition of two isoenzymes: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Prostaglandins are naturally occurring fatty acid derivatives with both pathological and physiological roles. Prostaglandin E₂ (PGE₂) is a potent vasodilator that causes erythema and edema and sensitizes tissues to pain- and inflammation-producing mediators such as histamine and bradykinin. PGE₂ is also a potent pyrogenic.

PE is a sympathomimetic amine that acts predominantly by a direct effect on α -adrenergic receptors. In therapeutic doses, the drug has no substantial stimulant effect on the β -adrenergic receptors of the heart (β_1) and does not stimulate β -adrenergic receptors of the bronchi or peripheral blood vessels (β_2). It is believed that α -adrenergic effects result from the inhibition of the production of cyclic adenosine-3',5'-monophosphate by inhibition of the enzyme adenylyl cyclase.

CHLOR, a classical H₁-receptor antagonist (antihistamine), has been available for more than 40 years as a nonprescription medication for relief of allergic rhinitis symptoms. It has been shown to be effective against major histamine-mediated symptoms, *i.e.*, sneezing, itching and rhinorrhea.

This is a 505 (b) (2) application. The proposed indication is for the temporary relief of these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose, itchy, watery eyes, itching of the nose or throat, sneezing, nasal congestion, sinus pressure, headache, minor body aches, pains, and fever for adults and children 12 years and older.

2.2 General Clinical Pharmacology

2.2.1 What clinical studies were conducted to support this NDA?

This is a 505 (b) (2) application based on PK program only. No clinical efficacy and safety trial was conducted. A total of one human pharmacokinetic trial has been submitted in support of this NDA. Study AD-05-05 is a three-way crossover, food and formulation effect, relative bioavailability study with an earlier development caplet formulation containing IBU 200 mg, PE Hydrochloride 10 mg, and CHLOR Maleate 4 mg.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

IBU (racemate) and CHLOR were measured in human plasma. Please refer to Section 2.6 Analysis for analytical details.

For PE, total PE (unmetabolized plus PE converted from conjugated PE) was measured. The assay is deemed not acceptable based on DSI inspection findings. See Section 2.6 and Appendix 4.3 for details.

PE is extensively metabolized in humans. The exposure to unmetabolized (“free”) PE is in low ng/mL range. Therefore, historically total PE is measured for PK assessment. The relative contributions of PE and its conjugated metabolites to efficacy are not clear. New assay method was reported¹ that lowered the assay sensitivity to pg/mL range and it is possible to measure unmetabolized PE with the new analytical method for PK assessment. The Sponsor is recommended to develop a new assay method that quantifies “free” PE.

2.2.3 What are the PK characteristics of IBU and CHLOR in this new product?

See PK summary in sections 2.3 and 2.5.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response?

Gender effects on IBU and CHLOR pharmacokinetics were evaluated. For IBU, no apparent gender effect was observed for mean C_{max} and AUC as shown in Table 2.3.1.1. For CHLOR, females, on average, exhibited 26% and 17% greater C_{max} and AUCI, respectively, compared to males (Table 2.3.1.2). When bodyweight was taken into considerations, the differences were nonexistent for C_{max} between two genders and females showed about 6% lower exposure (AUCI) compared to males indicating that bodyweight may have contributed towards the differences observed.

Table 2.3.1.1 Mean (SD) IBU PK parameters by gender after single-dose administration of IBU+PE+CHLOR caplet under fasted state

| | Male | Female |
|--------------------------|---------------|---------------|
| N | 19 | 21 |
| C _{max} (µg/mL) | 19.78 (4.15) | 20.95 (4.43) |
| AUCL (µg*h/mL) | 71.13 (13.59) | 74.72 (14.77) |
| AUCI (µg*h/mL) | 72.33 (13.63) | 75.87 (14.75) |

¹ P. Ptacek, J. Klima, and J. Macek. Development and validation of a liquid chromatography–tandem mass spectrometry method for the determination of phenylephrine in human plasma and its application to a pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci*. 858(1-2):263-268, 2007.

Table 2.3.1.2 Mean (SD) CHLOR PK parameters by gender after single-dose administration of IBU+PE+CHLOR caplet under fasted state

| | Male | Female | % Difference (Female vs. Male) | % Difference with Weight adjusted (Female vs. Male) |
|--------------------------|-----------------|----------------|--------------------------------|---|
| N | 19 | 21 | | |
| C _{max} (µg/mL) | 6.26 (1.38) | 7.88 (1.42) | +26 | +1 |
| AUCL (µg*h/mL) | 140.06 (46.6) | 158.11 (55.68) | +13 | -9 |
| AUCI (µg*h/mL) | 155.45 (182.21) | 182.21 (77.68) | +17 | -6 |

2.4 Extrinsic Factors

Not applicable

2.5 General Biopharmaceutics

2.5.1 Is there a formulation effect for the proposed combination drug product?

No. The data presented in Tables 2.5.1.1 and 2.5.1.2 suggest no formulation effect for both IBU and CHLOR pharmacokinetics as assessed by relative bioavailability of the new combination caplet formulation to single ingredient products administered together. The 90% confidence intervals for both AUC and C_{max} of IBU and CHLOR were found to be within the bioequivalence limits of 80-125%. The time to peak plasma concentration (T_{max}) values were also similar between the treatments.

Table 2.5.1.1. Mean (SD) IBU Pharmacokinetic Parameters (N=40) and Statistical Analysis

| | AUCL (mcg*h/mL) | AUCI (mcg*h/mL) | C _{max} (mcg/mL) | T _{max} (h) |
|---|-----------------------|-----------------------|---------------------------|----------------------|
| Mean (SD) | | | | |
| Treatment A | 73.01 (14.16) | 74.19 (14.16) | 20.40 (1.05) | 2.17 (1.05) |
| Treatment C | 73.31 (18.37) | 74.60 (18.22) | 1.80 (0.94) | 1.80 (0.94) |
| Geometric Mean Ratio (90% Confidence Intervals)* | | | | |
| A / C % | 101.19 (96.11-106.54) | 100.86 (95.99-105.98) | 94.79 (85.86-104.65) | — |

* based on fitted log-transformed parameters

Treatment A: IBU+PE+CHLOR Caplet-fasted

Treatment C: Motrin IB tablet + Sudafed PE Tablet + Chlor-Trimeton Allergy Tablet - fasted

Table 2.5.1.2. Mean (SD) CHLOR Pharmacokinetic Parameters (N=40) and Statistical Analysis

| | AUCL (mcg•h/mL) | AUCI (mcg•h/mL) | C_{max} (mcg/mL) | T_{max} (h) |
|---|----------------------------|----------------------------|-------------------------------------|--------------------------------|
| Mean (SD) | | | | |
| Treatment A | 149.54 (51.73) | 169.50 (68.97) | 7.11 (1.61) | 4.03 (1.25) |
| Treatment C | 158.03 (51.60) | 175.33 (62.47) | 7.47 (1.66) | 3.86 (1.38) |
| Geometric Mean Ratio (90% Confidence Intervals)* | | | | |
| A /C % | 93.81 (90.73-96.99) | 94.98 (91.57-98.52) | 95.18 (92.05-98.41) | — |

* based on fitted log-transformed parameters

Treatment A: IBU+PE+CHLOR Caplet-fasted

Treatment C: Motrin IB tablet + Sudafed PE Tablet + Chlor-Trimeton Allergy Tablet - fasted

Formulation effect within gender was also evaluated by estimating separately for males and females the ratios of log-transformed PK data along with 90% confidence intervals for IBU and CHLOR as shown in Table 2.5.1.3. Except for IBU C_{max} in females, bioequivalence was achieved for all PK comparisons within gender, i.e. 90% CIs fell within 80-125% BE limits. One of the plausible reasons for not achieving BE for IBU C_{max} could be that the analysis involved smaller number of female subjects (n=21) that may not have adequate power to declare BE. In general, females exhibited a slightly higher peak plasma concentration of IBU (Table 2.5.1.1). Considering these factors, it can be concluded that this slight deviation from the lower limit of the BE interval is considered clinically not relevant. Therefore, it is concluded that there is no gender-dependent formulation effect on the systemic exposure of IBU and CHLOR for this combination caplet.

Table 2.5.1.3. Gender based evaluation of formulation effect: Geometric mean ratios (90% confidence interval) of PK parameters of IBU and CHLOR following administration of the proposed combination caplet (test) vs. single ingredients administered together (reference) under fasted state

| Actives | IBU | | CHLOR | |
|------------------------|-----------------------|-----------------------|---------------------|-----------------------|
| | Males (n=19) | Females (n=21) | Males (n=19) | Females (n=21) |
| C_{max} | 103.2 (87.7-121.5) | 87.0 (76.8-98.4) | 94.3 (89.9-99.0) | 96.0 (91.4-100.8) |
| AUCL | 103.7 (95.6-112.4) | 98.4 (92.7-104.4) | 94.0 (89.9-98.3) | 93.6 (89.0-98.4) |
| AUCI | 104.4 (95.9-113.7) | 98.5 (93.0-104.4) | 94.4 (90.1-98.8) | 95.5 (90.3-101.0) |

2.5.2 Is there a potential for drug-drug interaction between CHLOR and PE, IBU and PE, and IBU and CHLOR?

The triple combination of an analgesic, decongestant, and antihistamine and double combinations of antihistamine / decongestant and antihistamine / analgesic are all considered Category I

combinations, i.e. permitted combinations as per the OTC monograph (21CFR 341.40). There are many three-ingredient combination products containing an analgesic / decongestant / antihistamine currently marketed OTC, including the triple combination of IBU/PSE/CHLOR from Wyeth that the company seeks to replace with a new triple combination containing PE as the decongestant of choice instead of pseudoephedrine (PSE). Lack of PK interaction between IBU, PSE and CHLOR was concluded in the Clinical Pharmacology review of NDA 21-441 for Advil Allergy Sinus Caplets (reference: Dr. Tapash Ghosh's review dated 08/08/2002). Therefore, a lack of potential for drug-drug interaction between CHLOR and PE is accepted per OTC monograph and drug-drug interaction between IBU and CHLOR as per previous conclusions by the Agency.

The potential interaction between IBU and PE was addressed [REDACTED] (b) (4)

[REDACTED] Dr. Zhang concluded no significant change in IBU systemic exposure (AUC and Cmax) when these two drug components are combined relative to IBU alone. However, there is a clear trend towards longer Tmax from the double combination (IBU/PE) [REDACTED] (b) (4) as well as triple combination (IBU/PE/CHLOR) caplet (this NDA) compared to historical IBU PK data obtained from NDA 19-842, NDA 20-418, and NDA 20-135 where Nuprin® 200 mg IB tablet (IBU alone) was studied as the reference drug. The average Tmax under fasted state from the historical Nuprin® (IBU alone) data in male subjects was 1.26 h compared to 1.86 h and 2.17 h for the double and triple combination caplets, respectively. However in a previous NDA 21-441 (refer to Dr. Tapash Ghosh's Review dated 08/08/2002) from Wyeth for Advil Allergy Sinus Caplets (the drug which the new proposed caplet is seeking to replace), Nuprin® alone treatment arm exhibited a mean Tmax of 1.88 h, which is much closer to 2.17 h found in study AD-05-05 (this NDA). Although a clear trend for longer Tmax is evident, a precise estimation of the magnitude is difficult to make in cross-study comparisons.

2.5.3 What is the likely clinical impact of delayed IBU Tmax for the new formulation?

Because no clinical trial was conducted with this new combination product of IBU/PE/CHLOR, the IBU PK/PD models for analgesic and antipyretic pain were used to help understand the likely impact of delayed Tmax of IBU for this combination product. Both in-house analysis as well as literature data suggested that for both analgesic (dental pain) and antipyretic (febrile fever) PK/PD models of IBU, the EC₅₀ is in the range of 6-10 µg/mL. In general, for pain relief or fever reduction, reaching EC₅₀ (i.e., > 6-10 µg/mL) by 30 minutes is highly desirable. We determined percentage of subjects who had plasma IBU levels above 6 and 10 µg/mL at 30 and 60 minutes (Table 2.5.3.1) following administration of the proposed combination caplet under fasted state to estimate likely clinical effect of IBU.

Individual data from historical IBU PK data (NDA 20-135, Biostudy 125) were retrieved from NDA 20-135 review and used for cross-study comparisons. Delayed IBU Tmax in IBU/PE combination product compared to IBU single ingredient product (Nuprin) led to lower percentage of subjects reaching EC₅₀ at early time points (< 1 hr). As shown in Table 2.5.3.1, 27% and 42% of the subjects had IBU plasma concentrations ≥10 µg/mL at 30 min and 60 min, respectively, following single-dose administration of the combination caplet. In comparison, historical IBU

PK data from IBU single ingredient Nuprin®

(b) (4)

) exhibited that 55% and 86% of the subjects had IBU plasma concentrations above 10 µg/mL at 30 min and 60 min, respectively. Therefore, the number of subjects achieving IBU concentrations at or above EC₅₀ at early time points from the combination caplet was markedly less (~50% lower) compared to that from Nuprin. Similar trend is found when 6 µg/mL was set to be the benchmark for comparison as shown in Table 2.5.3.1. Depending on the importance of onset of analgesic/antipyretic for the proposed indication, the delayed Tmax of IBU for the IBU/PE/CHLOR combination caplet may be clinically undesirable.

Table 2.5.3.1. Cross-study comparisons of IBU plasma concentrations at 30 min and 60 min in subjects receiving IBU/PE/CHLOR caplet (NDA 22-113) and Nuprin® (IBU alone from NDA 20-135: historical data) under fasted state.

| | NDA 22-113 (this submission) | | NDA 20-135 (historical) | |
|--------------------------|------------------------------|---------------|-------------------------|---------------|
| | 30 min | 60 min | 30 min | 60 min |
| % of Subjects ≥ 6 µg/mL | 45 (18/40) | 70 (28/40) | 77 (17/22) | 92 (22/24) |
| % of Subjects ≥ 10 µg/mL | 27 (11/40) | 42 (17/40) | 55 (12/22) | 86 (19/24) |
| Mean (µg/mL) | 7.3 | 10.1 | 13.8 | 16.3 |
| SD (µg/mL) | 5.2 | 6.9 | 9.7 | 6.7 |
| CV% | 71.8 | 68.0 | 33.8 | 29.0 |

2.5.4 What is the effect of food on the bioavailability of the drug from the dosage form?

No food effect was detected for both IBU and CHLOR since the 90% confidence intervals around the ratios of AUCL, AUCI and C_{max} for the comparison of IBU/PE/CHLOR caplet under fed vs. fasted states were all within the 80-125% bioequivalence limit (Tables 2.5.4.1-2). Mean Tmax values for IBU and CHLOR between fed and fasted states were generally comparable.

Table 2.5.4.1. Mean (SD) IBU Pharmacokinetic Parameters (N=40) and Statistical Analysis

| | AUCL (mcg•h/mL) | AUCI (mcg•h/mL) | C _{max} (mcg/mL) | T _{max} (h) |
|---|------------------------|------------------------|------------------------------|-------------------------|
| Mean (SD) | | | | |
| Treatment A | 73.01 (14.16) | 74.19 (14.16) | 20.40 (1.05) | 2.17 (1.05) |
| Treatment B | 65.70 (14.58) | 67.26 (14.65) | 19.27 (6.76) | 1.91 (1.41) |
| Geometric Mean Ratio (90% Confidence Intervals)* | | | | |
| B/A % | 89.64 (85.14-94.38) | 89.61 (85.24-94.21) | 90.21 (81.72-99.58) | — |

* based on fitted log-transformed parameters
 Treatment A: IBU+PE+CHLOR Caplet-fasted
 Treatment B: IBU+PE+CHLOR Caplet-fed

Table 2.5.4.2. Mean (SD) CHLOR Pharmacokinetic Parameters (N=40) and Statistical Analysis

| | AUCL (mcg•h/mL) | AUCI (mcg•h/mL) | C _{max} (mcg/mL) | T _{max} (h) |
|---|--------------------------|--------------------------|------------------------------|-------------------------|
| Mean (SD) | | | | |
| Treatment A | 149.54 (51.73) | 169.50 (68.97) | 7.11 (1.61) | 4.03 (1.25) |
| Treatment B | 151.72 (52.86) | 171.80 (66.28) | 7.21 (1.55) | 3.73 (1.57) |
| Geometric Mean Ratio (90% Confidence Intervals)* | | | | |
| B/A % | 101.40 (98.07-104.83) | 101.93 (98.27-105.72) | 101.80 (98.46-105.26) | — |

* based on fitted log-transformed parameters
 Treatment A: IBU+PE+CHLOR Caplet-fasted
 Treatment B: IBU+PE+CHLOR Caplet-fed

2.5.5 Did the sponsor use to-be-marketed formulation in the pivotal bioequivalence (BE) trials? If not, was an appropriate bridge study conducted to compare the formulation?

No. The proposed to-be-marketed caplet is not the formulation investigated in the pivotal BE study AD-05-05. The to-be-marketed formulation contains 0.25% propyl gallate, whose function is to improve the stability of PE in the caplets, whereas the clinical formulation does not contain propyl gallate. To support a waiver of *in-vivo* bioequivalence study, the applicant submitted *in-vitro* dissolution data with f₂ analysis according to the agreement made with the FDA in the pre-NDA meeting (March 19, 2007). The adequacy of the dissolution data is being judged by the CMC reviewer at the time of this review.

2.6 Analytical Section

2.6.1 Were the analytical methods used to determine IBU in plasma adequately validated?

Yes. The method is summarized in Table 2.6.1.1. Briefly, a 500-µL sample aliquot is fortified with 50 µL of internal standard working solution. The sample is liquid-liquid extracted with organic solvent. The organic layer is transferred into clean tubes containing keeper solution. The eluate is evaporated and the remaining residue is reconstituted with 200 µL of mobile phase. A 50-µL volume of the final extract is injected and analyzed via HPLC with ultraviolet absorbance detection.

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 IBU in human plasma.

| Analytes | Internal Standard | Analytical Method | QC Samples | LLOQ | Linear Range | Stability in plasma at -20°C |
|-----------|-------------------|------------------------|-----------------------|-----------|---------------------------------------|------------------------------|
| Ibuprofen | | (b) (4) Method P046.04 | 0.2, 0.4, 4, 40 µg/mL | 0.2 µg/mL | 0.2-50 µg/mL (R ² ≥ 0.998) | > 4 months |

Table 2.6.1.2. Assessment of accuracy and precision of assay methodology for IBU.

| | IBU |
|-----------------------|---------------|
| Intra-Assay Accuracy | -1.5% to 5.0% |
| Intra-Assay Precision | 2.0% to 7.2% |
| | |
| Inter-Assay Accuracy | 4.5% to 7.0% |
| Inter-Assay Precision | -6.0% to 3.3% |

2.6.2 Were the analytical methods used to determine PE in human plasma adequately validated?

No. The DSI inspection identified major flaws associated with the analytical method, LCMS 247 V2, used for quantifying the total PE levels (see DSI report by Dr. O'Shaughnessy and appendices). The analysis was conducted (b) (4).

In this method, a 50.0-µL sample aliquot is fortified with 150 µL of internal standard working solution and 50 µL of β-glucuronidase solution, pH 5.5. The samples are then incubated at 37 °C for 2.5 hours. The analytes are isolated by solid phase extraction using 10-mg Waters Oasis WCX 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 directly injected and analyzed via HPLC with MS/MS detection. Detection is by positive ion electrospray tandem mass spectrometry using a Sciex API 3000. For multiple reaction monitoring (MRM), the transitions monitored are 168.1 to 150.1 for PE and 171.1 to 153.1 for PE-d3.

The (b) (4) analytical lab identified the assay problem when a lack of reproducibility was observed with the incurred samples in July 2007 with a separate BE study (AQ-06-06), not submitted to (b) (4) 22-113. (b) (4) own investigation revealed that the combination of two main factors namely 1) incomplete hydrolysis of the PE conjugates (sulfates and glucuronides) and 2) partial degradation of unconjugated PE as it was being formed, led to lack of reproducibility observed with PK repeat samples. In addition, the DSI inspection also found that the quality control (QC) samples used for run acceptance were different from the subject samples in that the QCs were spiked with unconjugated PE only. Pooled incurred plasma samples were used as hydrolysis controls to verify that hydrolysis procedure was conducted. But variability for these samples were >20% and no acceptance criteria were in-place to reject a run. These factors

resulted in underestimated values and an increase in variability for *total* PE concentration in study samples. Refer to DSI reviewer’s memo (Appendix 4.3) for additional details.

Because accuracy was not assured due to flawed bioanalytical method for total PE, the reported total PE concentrations for Study AD-05-05 are not reliable for exposure and bioequivalence determination. A disturbing observation was noted from the DSI inspection that neither Wyeth nor (b) (4) informed FDA prior to the inspection that the assay used for Study AD-05-5 was flawed although this information was available before the original NDA submission.

The analytical lab, (b) (4), subsequently optimized the PE method (LCMS 257 version 3.01) and reanalyzed a subset of subject samples from Study AD-06-06 with the method optimized for PE glucuronide. Wyeth submitted an amendment providing an assessment of (b) (4) investigation of the PE bioanalytical method problems and sample analyses for studies AD-06-06 and AD-05-05 and concluded lack of impact of PE assay issues on the bioequivalence conclusions of the study AD-05-05. Refer (b) (4) Dr. O’Shaughnessy’s DSI report and appendices for further discussion of reasons from the Agency’s side for not accepting Wyeth’s assessment.

2.6.3 Were the analytical methods used to determine CHLOR in human plasma adequately validated?

Yes. The method is summarized in Table 2.6.3.1. Briefly, a 50 mL sample aliquot is transferred to a conical-bottom, 96-well plate and fortified with 25 mL of internal standard working solution. A 350-mL volume of acetonitrile is added to precipitate protein. Upon centrifugation, a 50 µL supernatant solution is then transferred to a new conical-bottom, 96-well plate and diluted with 400 mL of 0.1% formic acid solution. A 30-mL volume of the final extract is injected and analyzed via HPLC with MS/MS detection.

The method is adequately validated to show selectivity and sensitivity. The performance was acceptable (Table 2.6.3.2). The DSI inspection did not identify any major issues, although some minor issues were identified and communicated to the analytical site, most of which were subsequently resolved. Refer to DSI report for further details.

Table 2.6.3.1. Summary of Analytical Method for CHLOR in human plasma.

| Analytes | Internal Standard | Analytical Method | QC Samples | LLOQ | Linear Range | Stability in plasma at -20°C |
|------------------|-------------------|--------------------------------|------------------------|------------|---------------------------------------|---|
| Chlorpheniramine | (b) (4) | (b) (4) Method LCMS 214 V 1.00 | 0.25, 0.5, 5, 40 ng/mL | 0.25 ng/mL | 0.25-50 ng/mL (R ² ≥ 0.99) | ~ 250 days (although study samples stored at -70°C) |

Table 2.6.3.2. Assessment of accuracy and precision of assay methodology for CHLOR.

| | CHLOR |
|-----------------------|----------------|
| Intra-Assay Accuracy | -12.2% to 9.3% |
| Intra-Assay Precision | 1.3% to 12.5% |
| | |
| Inter-Assay Accuracy | -1.1% to 3.7% |
| Inter-Assay Precision | 4.5% to 11.6% |

3 Labeling Recommendation:

The label for an OTC product does not contain PK information. Refer to the appropriate reviews from ONP/DNCE for details of labeling review comments. Delay in T_{max} may need to be appropriately reflected in the label for optimal use of this product.

4 APPENDIX

4.1 ANNOTATED PROPOSED PACKAGE INSERTS from the Sponsor

(b) (4)

**Ibuprofen 200 mg>>Pain Reliever/Fever Reducer (NSAID)
Phenylephrine HCl 10 mg>>Nasal decongestant
Chlorpheniramine maleate 4 mg>>Antihistamine**

(b) (4)

| <i>Annotations</i> |
|---|
| 21 CFR 201.66(c)(2) & (c)(3) 21 CFR 341.12 (c)/341.72 (a); NDA 19-771 21 CFR 341.20(a)(1) 21 CFR 341.80(a); 21 CFR 341.40(c) (53 FR 30561) 21 CFR 341.85(a) (53 FR 30562); FDA letter of 7/15/05 |
| 21 CFR 201.66 (c)(4); 21 CFR 341.72 (b)(1) 21 CFR 341.80 (b)(1)(ii) NDA 21-441 21 CFR 341.85 (b)(2) (53 FR 30562) 21 CFR 341.80 (b)(2)(iv) & (v) |

(b) (4)

21 CFR 201.66 (c)(5)

21 CFR 201.66 (c)(5)(ii)(B) /
FDA Class Labeling (Allergy
Warning) for ibuprofen

[FDA letter of 7/15/05](#)

21 CFR 201.322 (a)(2)

21 CFR 201.66 (c)(5)(iii)

FDA Class Labeling (Allergy
Warning) for ibuprofen

21 CFR 341.80 (c)(1)(i)(D)

[FDA letter of 7/15/05](#)

(b) (4)

21 CFR 201.66 (c)(5)(iv)
21 CFR 341.72 (c)(2)
21 CFR 341.80 (c)(1)(i)(C)
NDA 19-771
21 CFR 341.72 (c)(2) / 341.80
(c)(1)(i)(C)

[FDA letter of 7/15/05](#)

21 CFR 201.66 (c)(5)(v)
NDA 19-771
21 CFR 341.72 (c)(3)
[FDA letter of 7/15/05](#)
[FDA letter-4/17/2006](#)
Published studies

21 CFR 201.66 (c)(5)(vi)
21 CFR 341.72 (c)(3)
21 CFR 341.72 (c)(1)
NDA 19-771
[FDA letter of 7/15/05](#)

(b) (4)

21 CFR 201.66 (c)(5)(vii)
FDA Class Labeling (Allergy
Warning)
21 CFR 341.85 (c)(3)(i) (53
FR 30563)
21 CFR 341.80 (c)(1)(i)(A)
NDA 19-771
[FDA letter of 7/15/05](#)

21 CFR 201.66 (c)(5)(ix)
21 CFR 330.2
21 CFR 201.63 (a)
NDA 19-771
21 CFR 201.63 (e)
21 CFR 201.66 (c)(5)(x)
21 CFR 330.1 (g)

21 CFR 201.66 (c)(6)
21 CFR 201.5
21 CFR 341.85 (d) (53 FR
30563)
Study #AD-99-02
NDA 19-771

21 CFR 201.66 (c)(7)
NDA 19-771

21 CFR 201.66 (c)(8)

21 CFR 201.66 (c)(9)

Format/contents:
21 CFR 201.66 (c) & (d);
21 CFR 330.1(i) & (j)
Other references:
21 CFR 341 Cough/cold FM

4.2 Individual Study Review

Protocol # P086

Study Type: Food/Formulation effect study.

Title: A Three-Way Crossover, Food Effect/Formulation Effect, Bioavailability Study of a Caplet Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg, and Chlorpheniramine Maleate 4 mg

Clinical Investigator: Dr. Aziz Laurent, MD; PPD Development, Austin, TX 78744.

Study Dates: May 20, 2006 – June 13, 2006

Objectives:

- To characterize the rate and extent of absorption of ibuprofen (IBU), phenylephrine hydrochloride (PE), and chlorpheniramine maleate (CHLOR) from a caplet containing IBU 200 mg, PE 10 mg, and CHLOR 4 mg when administered under fasted and fed conditions;
- To characterize the rate and extent of absorption of IBU, PE, and CHLOR from a caplet containing IBU 200 mg, PE 10 mg, and CHLOR 4 mg compared to IBU 200 mg, PE 10 mg, and CHLOR 4 mg single entity products administered concomitantly.

Study Design and Method: A single-center, randomized, open-label, single-dose, three-way crossover bioavailability study in 41 healthy subjects (19 males and 22 females). The three treatments were as follows:

Treatment A: one combination caplet containing IBU 200 mg, PE 10 mg, and CHLOR 4 mg administered orally under fasted conditions,

Treatment B: one combination caplet containing IBU 200 mg, PE 10 mg, and CHLOR 4 mg administered orally under fed conditions,

Treatment C: one Motrin® IB tablet (IBU 200 mg/tablet), one Sudafed® PE tablet (PE 10 mg/caplet), and one Chlor-Trimeton® Allergy tablet (CHLOR 4 mg) orally administered concomitantly under fasted conditions.

Criteria for Evaluation: Key PK parameters (AUC_L, AUC_I, C_{max}) of IBU, PE and CHLOR. Additional PK parameters include T_{max}, Kel, Vd, CL and t_{1/2}.

Blood sampling times: Pre-dose (0), 15, 30, 45, 60, 75, 90 minutes and 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, and 72 hours post-dose.

Analytical Methodology

Assay Method: HPLC/UV detector (IBU), LC/MS/MS (CHLOR)

Assay Sensitivity (standard curves): 0.2 to 50 µg/mL (IBU), 0.25 to 50 ng/mL (CHLOR)

The assay method for PE has major flaws as determined by DSI inspection and hence not acceptable.

Therefore, it is not described here (see Appendix 4.3 for details)

Data Analysis: Descriptive statistics were computed for pertinent pharmacokinetic parameters for each treatment. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference for C_{max}, AUC_{0-t} and AUC_{0-∞}. C_{max} and AUCs were natural-log (ln) transformed prior to analysis. Bioequivalence and the absence of a food effect were declared if the 90% two-sided CI for the ratio was between 0.8 and 1.25 for log transformed PK parameters.

The following comparisons were made:

Food effect: IBU + PE + CHLOR caplet fed vs. fasted (reference);

Formulation effect: IBU + PE + CHLOR caplet fasted vs. IBU, PE, and CHLOR single entity products administered concomitantly (reference).

Results:

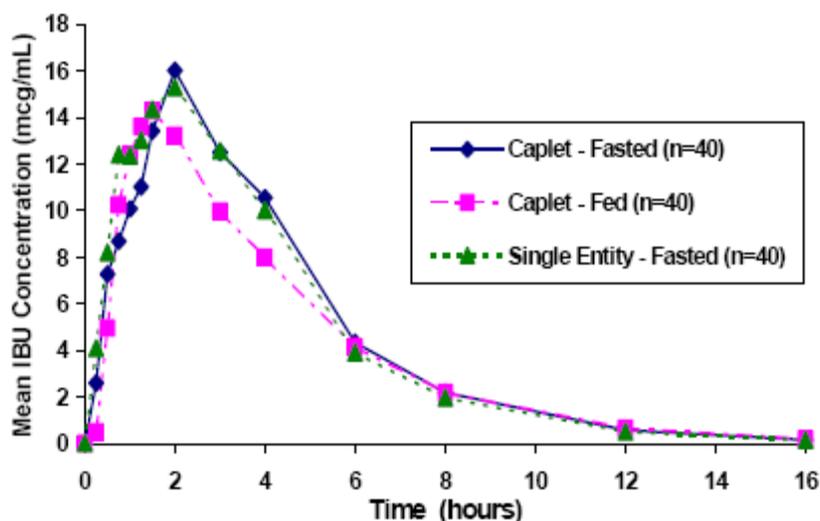
Study Population: Forty-one (41) healthy subjects (19 males and 22 females) were enrolled of which 40 completed all three study periods and one subject withdrew consent at the 45-minute time-point during Period I due to difficulty in blood draws; thus 40 subjects were included in the PK analysis and 41 were included in the safety analysis.

Pharmacokinetics: Due to unacceptable PE bioanalytical assay method, PE pharmacokinetic results are not described here. Only IBU and CHLOR data are presented.

Ibuprofen

Mean plasma IBU concentration vs. time profiles are presented in Figure 1. As shown, the mean plasma concentrations of IBU were similar among the treatments.

Figure 1. Mean (n=40) plasma concentration vs. time profiles of IBU after single-dose administration of one combination caplet (IBU 200 mg + PE 10 mg + CHLOR 4 mg) under fasted and fed conditions, and single entity products administered concomitantly under fasted conditions to healthy male and female adult subjects.



The plasma pharmacokinetic parameters of IBU and summary statistics including geometric mean ratios of AUCL, AUCI, and C_{max} along with 90% confidence intervals for the administration of the combination caplet under fasted and fed states, and the single entity products administered concomitantly under fasted state are provided in Table 1. Comparative analyses of (combination fasted vs. concomitant fasted) and (fed vs. fasted) evaluate formulation and food interactions, respectively. The data listed in Table 1 indicate lack of either interaction as evidenced by the geometric mean ratios (along with 90% confidence limits) for AUCL, AUCI, and C_{max} contained within the bioequivalence criterion of 80 to 125%.

Table 1. Mean (n=40) PK parameters of IBU after single-dose administration of one combination caplet (IBU 200 mg + PE 10 mg + CHLOR 4 mg) under fasted and fed conditions, and single entity products administered concomitantly under fasted conditions to healthy male and female adult subjects.

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

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

^: Based on fitted log transformed parameters.

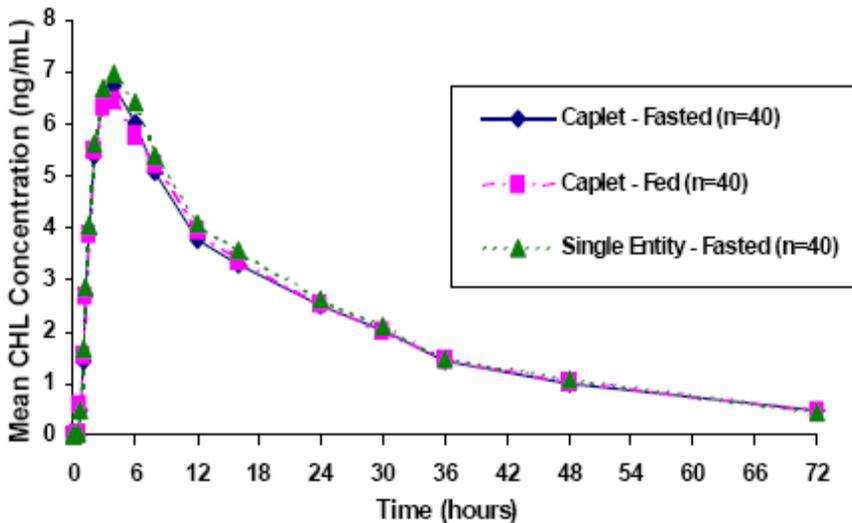
*: Reference product.

#: Subject No. 108's concentration for treatment B did not exhibit a log linear elimination phase and thus AUCI and t_{1/2} could not be computed. Consequently, the ratio and 90% CI for Ln AUCI, as well as the summary statistics for AUCI and t_{1/2} for treatment B were based on 39 subjects.

Chlorpheniramine

Mean plasma CHLOR concentration vs. time profiles are presented in Figure 2. As shown, the mean plasma concentrations of CHLOR were similar among the treatments.

Figure 2. Mean (n=40) plasma concentration vs. time profiles of CHLOR after single-dose administration of one combination caplet (IBU 200 mg + PE 10 mg + CHLOR 4 mg) under fasted and fed conditions, and single entity products administered concomitantly under fasted conditions to healthy male and female adult subjects.



The plasma pharmacokinetic parameters of CHLOR and summary statistics including geometric mean ratios of AUCL, AUCI, and C_{max} along with 90% confidence intervals for the administration of the combination caplet under fasted and fed states, and the single entity products administered concomitantly under fasted state are provided in Table 2. Comparative analyses of (combination fasted vs. concomitant fasted) and (fed vs. fasted) evaluate formulation and food interactions, respectively. The data listed in Table 2 indicate lack of either interaction as evidenced by the geometric mean ratios (along with 90% confidence limits) for AUCL, AUCI, and C_{max} contained within the bioequivalence criterion of 80 to 125%.

Table 2. Mean (n=40) PK parameters of CHLOR after single-dose administration of one combination caplet (IBU 200 mg + PE 10 mg + CHLOR 4 mg) under fasted and fed conditions, and single entity products administered concomitantly under fasted conditions to healthy male and female adult subjects.

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

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

[^]: Based on fitted log transformed parameters.

*: Reference product.

Safety:

Throughout the study, 15 subjects reported 21 AEs. The most common AEs among all treatments were headache (four incidences across treatments), followed by dizziness and dyspepsia (three incidences across treatments for each). All but two AEs were rated as mild; the other two were rated as moderate. All but two AEs were unrelated to study medications. No notable differences among the treatments were seen in the individual AE rates. There were no serious AEs noted during the study. None of the subjects dropped out due to an AE. There were no clinically significant changes in physical examination, including vital signs at the conclusion of the study.

Conclusions:

The rate and extent of absorption of IBU and CHLOR were equivalent when the IBU+PE+CHLOR combination caplet was administered under fasted and fed conditions, hence no evidence of food effect. Under fasted conditions, the IBU+PE+CHLOR caplet had an equivalent rate and extent of absorption of IBU and CHLOR relative to the single entity marketed products containing IBU (Motrin IB), PE (Sudafed PE), and CHLOR (Chlor-Trimetron Allergy) indicating no formulation interaction. All three ingredients were well tolerated whether taken alone or in combination under fasted and fed conditions.

DSI Reviewer's Memo (Attachments are omitted)

MEMORANDUM

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

DATE: May 2, 2008

FROM: Jacqueline A. O'Shaughnessy, Ph.D.
Mark J. Seaton, Ph.D.
Samuel Chan, Pharm.D.
Division of Scientific Investigations (HFD-48)

THROUGH: CT. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-113 for (b)(4)
(b)(4) (Ibuprofen 200 mg/Phenylephrine
HCl 10 mg/Chlorpheniramine Maleate 4 mg) (b)(4),
Sponsored by Wyeth Consumer Healthcare

TO: Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
(DNCE)

At the request of DNCE, the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Protocol AD-05-05: A Three-Way Crossover, Food Effect/Formulation Effect, Bioavailability Study of a Caplet Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 1 mg, and Chlorpheniramine Maleate 4 mg

The clinical and analytical portions of this study were conducted (b)(4)
(b)(4)

Inspection of the (b)(4) clinical site (b)(4) and the (b)(4) analytical site (b)(4) did not reveal any significant deficiencies; Form 483 was not issued at either site. Following the inspection at the (b)(4) facility in (b)(4), Form 483 was issued. DSI received (b)(4) response to the Form 483 on April 8, 2008. The objectionable

items and our evaluation are the following:

- 1. The bioanalytical method for total phenylephrine is flawed and the reported subject sample concentrations are not accurate.**

Subsequent to the conduct and reporting of Study AD-05-05, (b) (4) determined that their method (LCMS 257 version 2) significantly underestimated the concentration of total phenylephrine (PE) present in the subject samples. Neither Wyeth nor (b) (4) informed the Agency that the reported results were not accurate prior to the DSI inspection. The bioanalytical method for Study AD-05-05 measured total PE. This involved enzyme hydrolysis of PE conjugates (sulfate, glucuronide) present in plasma samples from subjects dosed with PE (i.e., incurred samples). (b) (4) determined that their method was flawed following an investigation initiated in June 2007.¹ (b) (4) investigation found that total PE concentrations were not accurately measured due to incomplete hydrolysis of the PE-conjugates and instability of unconjugated PE under the hydrolysis conditions (Attachment 1). The inspection also found that the quality control (QC) samples used for run acceptance were different from the subject samples in that the QCs were spiked with unconjugated PE only.

Because accuracy was not assured, the reported total PE concentrations for Study AD-05-05 are not reliable. Please note that this finding applies to all studies conducted with (b) (4) method LCMS 257 version 2 for total PE, including Wyeth Study AQ-05-03 submitted to (b) (4) (b) (4)

According to (b) (4) the PE method was subsequently optimized (LCMS 257 version 3.01). On September 7, 2007 Wyeth requested reanalysis of a subset of subject samples from Study AD-06-06

¹ The investigation was initiated to evaluate non-reproducibility observed between original and repeat results (i.e., pharmacokinetic repeats) for subject samples from a different Wyeth study (not Study AD-05-05 from NDA 22-113). Email correspondence provided by (b) (4) indicated that (b) (4) informed Wyeth of the method problem and investigation on July 19, 2007.

² Please refer to DSI memo dated April 10, 2008. Please note that (b) (4) also conducted studies for (b) (4) with the flawed method.

with the method optimized for PE glucuronide.³ (The DSI inspection did not audit data related to the revised method). The original results were significantly underestimated compared to the repeat results, with differences ranging from approximately 100-4300% (Attachment 2). Wyeth did not request reanalysis of the three other studies that (b)(4) conducted for them with the flawed method (Studies AQ-05-03, AD-05-05, and AQ-06-08).

Contrary to Wyeth's assessment of this issue submitted after the DSI inspection, extrapolating the outcome of the reanalysis for Study AD-06-06 to other studies that used the flawed method is not justified as accuracy was not assured for the total PE concentrations reported from the flawed method. The claim made by (b)(4) and Wyeth that the degree of total PE concentration underestimation within a batch of samples processed together was consistent (i.e., that with-in batch samples underwent similar levels of hydrolysis) is not supported by the repeat data from Study AD-06-06 (Attachment 2). Specifically, the difference in original and repeat results **between samples within a subject** was highly variable. For example, the 0.25-8 hour samples for subjects 101 and 204 had differences ranging from 213-318% and 179-315%, respectively, between the original and repeat results. This does not demonstrate a similar level of underestimation within a batch. Furthermore, it should be noted that samples beyond 8 hours had even greater differences. In our view, extrapolating the results of reanalysis of a subset of subject samples from Study AD-06-06 to Study AD-05-05 and other Wyeth studies that were analyzed using the flawed original method is not justified.

In response to the Form 483, (b)(4) stated that they have amended and reissued to sponsors all final reports that used the flawed method to note the inaccuracy of the method. In the future, (b)(4) intends to notify FDA if they discover that

³ The optimized method included QCs spiked with PE-glucuronide and a surrogate incurred plasma QC pool (prepared with plasma and incurred urine containing both PE-sulfate and PE-glucuronide) with an analytically determined concentration of total PE to quantitatively evaluate assay performance. In contrast, the original method used a QC spiked with unconjugated PE, and an incurred plasma QC pool for a qualitative measure of hydrolysis. According to (b)(4) PE-glucuronide was not available commercially when they developed the original method, and PE-sulfate is not currently available commercially. The percentage of hydrolysis of PE-sulfate is not known absolutely.

previously reported study data is subsequently found to be unreliable.

- 2. The chlorpheniramine method was not evaluated for potential interference from concomitantly administered phenylephrine.**

In response to the Form 483, (b) (4) submitted the results of recently completed interference testing. No interference was noted (Attachment 3).

- 3. Chromatography integration parameters for several runs were changed multiple times without documenting the interim changes made.**

The audit trail for the chromatography software (Analyst 1.2) documented that changes were made but did not capture the actual parameters altered with each interim modification. Because the firm's procedures include setting integration parameters prior to calculating the resulting sample concentrations and applying the parameters across the run as a whole, the incomplete documentation should not have a significant impact.

In response to the Form 483, the firm stated that they currently use a revised version of the software (Analyst 1.4.2) that captures the details of interim changes.

- 4. The storage temperature of samples used to demonstrate the stability of chlorpheniramine in extracted samples was not documented. Some runs were injected the day after extraction.**

In response to the Form 483, (b) (4) repeated the extract stability experiment. No stability problem was noted for the storage duration of the study sample extracts (Attachment 4).

Conclusions

For the reasons stated above, the Division of Scientific Investigations concludes that the accuracy of total PE concentrations reported for Study AD-05-05 was not demonstrated. In this regard, the reliability of the reported total PE data for a bioequivalence assessment has not been assured.

In addition, it is objectionable that neither Wyeth nor (b) (4) informed FDA prior to the inspection that the assay used for Study AD-05-05 was flawed although this information was available before the original NDA submission.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Jacqueline A. O'Shaughnessy, Ph.D.
Mark J. Seaton, Ph.D.
Samuel Chan, Pharm.D.

Attachment 1: (b) (4) investigation, draft report
Attachment 2: Repeat result comparison, Wyeth Study AD-06-06
Attachment 3: Interference assessment for chlorpheniramine
Attachment 4: Extract stability for chlorpheniramine

Final Classification

(b) (4)

CC:

HFD-45/Vaccari
HFD-48/Himaya/O'Shaughnessy/Seaton/Chan/CF
OCP/DCP2/Partha Roy
ONP/DNCE/Robin Anderson
HFR-SW1575/Lorenz
HFR-CE8585/Laufenberg
HFR-CE2545/Milazzo
Draft: JAO 4/24/08
Edit: MJS/SC/SS
DSI 5825 O:\BE\eircover\22113we.phe.doc

(b) (4)

4.3 OCP Filing and Review Form

| Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i> | | | | |
|---|---------------------------|-----------------------------|--|--------------------------|
| <u>General Information About the Submission</u> | | | | |
| | Information | | Information | |
| NDA Number | 22-113 | Brand Name | (b) (4) | |
| OCP Division | DCP2 | Generic Name | Ibuprofen 200mg/ Phenylephrine HCl 10mg / Chlorpheniramine Maleate 4mg | |
| Medical Division | DPAP | Drug Class | Triple Combination (fever, allergy, cold) | |
| OCP Reviewer | Partha Roy | Indication(s) | temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose; itchy, watery eyes; itching of the nose or throat; sneezing; nasal congestion; sinus pressure; headache; minor aches and pains; fever | |
| OCP Team Leader (Acting) | Wei Qiu | Dosage Form | IR Caplet | |
| | | Dosing Regimen | 1 caplet q4h NMT 6 caplets/day | |
| Date of Submission (Letter date) | September 25, 2007 | Route of Administration | Oral | |
| Estimated Due Date of OCP Review | April 24, 2007 | Sponsor | Wyeth Consumer | |
| PDUFA Due Date | July 25, 2008 | Priority Classification | Standard | |
| Division Due Date | May 25, 2008 | Relevant NDA | (b) (4) | |
| <u>Clin. Pharm. and Biopharm. Information</u> | | | | |
| | "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 | 1 | | AD-05-05 |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| 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: | | | | |
| 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 | | | Single-dose food/formulation effect study |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | x | | | |
| Dissolution: | x | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | x | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 1 | | |

| Filability and QBR comments | | | |
|--|------------|--|--|
| | “X” if yes | Comments | |
| Application filable? | X | <p>Since DDI was not addressed in the original submission, a T-con was held on Nov 16, 2007. The lack of a cross-reference letter to (b) (4) regarding DDIs was an oversight on their part and it was sent via email on November 19, 2007.</p> <p>DSI inspection of Study AD-05-05 is recommended</p> <p>AD-05-05: A Three-Way Crossover, Food Effect/Formulation Effect, Bioavailability Study of a Caplet Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg, and Chlorpheniramine Maleate 4 mg</p> <p><u>Clinical Site:</u> PPD Development 7551 Metro Center Blvd., Suite 200 Austin, TX 78744</p> <div style="background-color: gray; width: 100%; height: 150px; margin-top: 10px;">(b) (4)</div> | |
| Comments sent to firm? | | | |
| QBR questions (key issues to be considered) | | <ol style="list-style-type: none"> 1. Formulation Effect: Demonstration of Bioequivalence between triple combination product (Wyeth) and co-administration (each components administered together). 2. Food effect (high fat meal) on the combination 3. Drug-drug interaction between three components | |
| Other comments or information not included above | | A bio-waiver for the to-be-marked formulation containing propyl gallate (PG) was requested. The chemist will review the dissolution data supporting the bio waiver. | |
| Primary reviewer Signature and Date | | Partha Roy 16 May 2007 | |
| Secondary reviewer Signature and Date | | Wei Qiu November 27, 2007 | |

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

/s/

Partha Roy
6/5/2008 11:10:12 AM
BIOPHARMACEUTICS

Wei Qiu
6/6/2008 09:49:52 AM
BIOPHARMACEUTICS

*Office of Clinical Pharmacology
New Drug Application Filing and Review Form*

General Information About the Submission

| | Information | | Information |
|----------------------------------|--------------------|-------------------------|--|
| NDA Number | 22-113 | Brand Name | (b) (4) |
| OCP Division | DCP2 | Generic Name | Ibuprofen 200mg/ Phenylephrine HCl 10mg / Chlorpheniramine Maleate 4mg |
| Medical Division | DPAP | Drug Class | Triple Combination (fever, allergy, cold) |
| OCP Reviewer | Partha Roy | Indication(s) | temporarily relieves these symptoms associated with hay fever or other upper respiratory allergies, and the common cold: runny nose; itchy, watery eyes; itching of the nose or throat; sneezing; nasal congestion; sinus pressure; headache; minor aches and pains; fever |
| OCP Team Leader (Acting) | Wei Qiu | Dosage Form | IR Caplet |
| | | Dosing Regimen | 1 caplet q4h NMT 6 caplets/day |
| Date of Submission (Letter date) | September 25, 2007 | Route of Administration | Oral |
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| PDUFA Due Date | July 25, 2008 | Priority Classification | Standard |
| Division Due Date | May 25, 2008 | Relevant NDA | (b) (4) |

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) - | | | | |
| <i>Healthy Volunteers-</i> | | | | |
| single dose: | x | 1 | | AD-05-05 |
| multiple dose: | | | | |
| <i>Patients-</i> | | | | |
| single dose: | | | | |
| 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: | | | | |
| 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 | | | Single-dose food/formulation effect study |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | x | | | |
| Dissolution: | x | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | x | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 1 | | |

| Filability and QBR comments | | |
|---|-------------------|--|
| | “X” if yes | Comments |
| Application filable? | X | <p>Since DDI was not addressed in the original submission, a T-con was held on Nov 16, 2007. The lack of a cross-reference letter to (b) (4) regarding DDIs was an oversight on their part and it was sent via email on November 19, 2007.</p> <p>DSI inspection of Study AD-05-05 is recommended</p> <p>AD-05-05: A Three-Way Crossover, Food Effect/Formulation Effect, Bioavailability Study of a Caplet Containing Ibuprofen 200 mg, Phenylephrine Hydrochloride 10 mg, and Chlorpheniramine Maleate 4 mg</p> <p><u>Clinical Site:</u> PPD Development 7551 Metro Center Blvd., Suite 200 Austin, TX 78744</p> <div style="background-color: gray; width: 100%; height: 150px; margin-top: 10px;">(b) (4)</div> |
| Comments sent to firm? | | |
| QBR questions (key issues to be considered) | | <ol style="list-style-type: none"> 1. Formulation Effect: Demonstration of Bioequivalence between triple combination product (Wyeth) and co-administration (each components administered together). 2. Food effect (high fat meal) on the combination 3. Drug-drug interaction between three components |
| Other comments or information not included above | | A bio-waiver for the to-be-marked formulation containing propyl gallate (PG) was requested. The chemist will review the dissolution data supporting the bio waiver. |
| Primary reviewer Signature and Date | | Partha Roy 16 May 2007 |
| Secondary reviewer Signature and Date | | Wei Qiu November 27, 2007 |

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

/s/

Partha Roy
12/4/2007 11:02:18 AM
BIOPHARMACEUTICS

Wei Qiu
12/4/2007 12:46:48 PM
BIOPHARMACEUTICS