Clinical Pharmacology Review

PRODUCT (Generic Name):	Naproxen sodium / Diphenhydramine hydrochloride
PRODUCT (Brand Name):	Aleve PM®
NDA:	205,352
DOSAGE FORM:	Tablet
DOSAGE STRENGTHS:	Naproxen sodium (220 mg) / DPH HCl (25 mg)
INDICATION:	Sleep aid for adults and adolescents as OTC product
SUBMISSION DATE:	3/20/2013
SPONSOR:	Bayer Healthcare
CP REVIEWER:	Xinning Yang, Ph.D., Bilal AbuAsal, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I

The applicant, Bayer HealthCare, seeks for approval of a nighttime analgesic/sleep-aid, fixed-dose combination, over-the-counter (OTC) drug product containing naproxen sodium 220 mg and diphenhydramine (DPH) hydrochloride 25 mg per tablet (film-coated). This product has been developed for the relief of occasional sleeplessness when associated with minor aches and pains, and help patients fall asleep and stay asleep. This product is indicated for adults and children 12 years of age and over, taken as a 2-tablet dose at bedtime.

Naproxen is a member of the non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic, anti-inflammatory, and antipyretic properties. DPH is an H_1-receptor antagonist used as a sedative, hypnotic, antihistamine, and antiemetic agent in some OTC products. Currently, there is no combination product available in the U.S. that combines naproxen sodium with DPH.

The clinical development program included one pilot efficacy study (13053), two pivotal efficacy studies (14837 and 15881), one multiple-dose safety study (15560), and one pharmacokinetic (PK) study (16135). These clinical studies were conducted to demonstrate the superior efficacy of naproxen sodium 440 mg/DPH HCl 50 mg combination product over its individual ingredients with similar safety and tolerability profiles. Fixed combination products, naproxen sodium 220 mg /DPH HCl 25 mg and naproxen 220 mg /DPH HCl 50 mg, were used

in these studies except Study 13053 where commercial products of Aleve® (naproxen sodium 220 mg tablet) and Benadryl® (DPH HCl 25 mg tablet) were administered concomitantly.

PK Study 16135 was a Phase 1, randomized, open-label, single-dose, 4-way cross-over study conducted in healthy adults. The objectives were to determine and compare the PK profiles of a single oral dose of naproxen sodium 220 mg/DPH HCl 25 mg (given as 2 tablets) taken under fasted and fed conditions with a single oral dose of either single ingredient product taken under fasted conditions and to evaluate for any potential drug-drug interactions between naproxen sodium and DPH in the combination product.

There is no drug-drug interaction for the combination product versus the single ingredient products. The 90% confidence intervals (CIs) of the geometric mean ratio (GMR) for naproxen C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$, following administration of naproxen sodium 440 mg/DPH HCl 50 mg vs. Aleve® 440 mg, were contained within the equivalence range of 80% and 125%. Similar results were observed for DPH, following administration of naproxen sodium 440 mg/DPH HCl 50 mg vs. commercially available Allergy Relief® 50 mg.

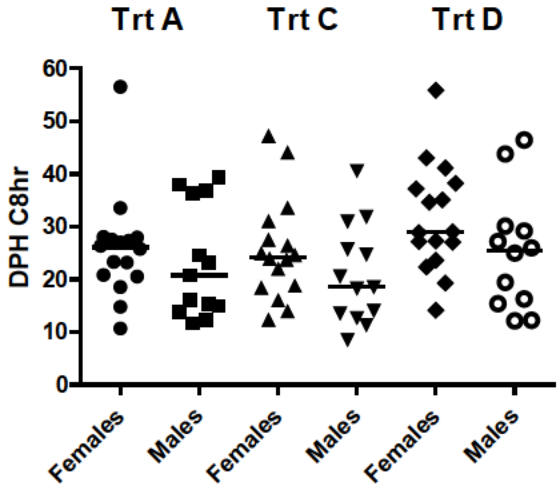
Food (high-fat meal) had no effect on the overall exposure (AUC) of naproxen or DPH in the combination product. Food intake decreased naproxen C_{max} by 19% and delayed its T_{max} to 3.0 (range: 0.75 – 6.0) hrs compared to 1.25 (range: 0.33 – 3.0) hrs under fasted conditions. In the proposed labeling, it is stated that, if taken with food, this product may take longer to work.

DPH is known to have hypnotic effects. Thus, there is a concern about its next-day residual effect, which may impair the ability to perform tasks like driving a vehicle or operating heavy machinery. The analysis focused on the concentration of DPH at 8 hours post-dose (C_{8hr}), which coincides with the expected wake time of general consumer population who take the combination product as a sleep-aid. The mean C_{8hr} of DPH was 23.4-28.8 ng/mL, after a single-dose administration of 50 mg DPH HCl either given as the combination product (under fasted and fed conditions) or as the single-ingredient product (Allergy Relief®, fasted). It appeared that females (N=16) had 14-30% higher C_{8hr} than males (N=13) (refer to the individual study review for details). In contrast, a literature study conducted in 37 young and elderly male and female healthy subjects who received a single dose of Benadryl® (containing 25 mg DPH HCl, fasted) showed that young females (N=10) had similar C_{8hr} as young males (N=10), while elderly females (N=10) had slightly lower C_{8hr} than elderly males (N=7) (Scavone J, et al., J Clin Pharmacol. 1998 Jul;38(7):603-9). Overall, females seemed to have approximately 20% higher DPH C_{8hr} than males.

Literature search identified a study evaluating the pharmacodynamics of DPH-induced drowsiness and changes in mental performance in 15 healthy males (Gengo F, et al. Clin Pharmcol Ther 1989;45:15-21). Subjects received single oral doses of 50 mg DPH HCl and placebo after overnight fasting in this double-blind crossover study. Cognitive impairment was assessed with an automobile driving simulator and digit symbol substitution scores, whereas

drowsiness was self-assessed on a visual analog scale. This study suggested that DPH concentration thresholds to produce drowsiness are lower (30.4 to 41.5 ng/rnL) than those needed to produce mental impairment (58.2 to 74.4 ng/mL). In Study 16135, the C_{8hr} of DPH in some subjects fell within the range of the threshold for drowsiness effect or above that, yet none of these subjects had C_{8hr} reaching the threshold for mental impairment effect (Figure 1). It should be noted that there are some limitations with this literature study: first, DPH HCl was administered in the morning. It is unknown whether the next-day residual effects and the corresponding thresholds will be similar after evening dosing, the time when Aleve PM will be given (at bedtime); secondly, the study only contained male subjects. The possibility of gender difference in pharmacodynamics of DPH cannot be excluded.

Figure 1. Plasma concentrations of DPH at 8 hours post-dose (C_{8hr}) grouped by gender for Treatments A (Aleve PM given under fasted condition), C (Allergy Relief (DPH HCl alone) administered after overnight fasting) and D (Aleve PM given under fed state). The horizontal bars represent the medians.



Additional analyses were performed to compare DPH plasma concentrations at 8 hours and 12 hours post-dose after administration of Aleve PM to other approved DPH-containing products in U.S. (e.g., Advil PM® caplet, Advil PM® liquid-gel, Motrin PM®). It was concluded that Aleve PM does not result in higher DPH concentrations than those marketed products.

In the proposed labeling for Aleve PM, it states that drowsiness will occur and consumers should avoid alcoholic drinks and do not drive a motor vehicle or operate machinery when using this product. Also, consumers should not take more than 2 tablets in 24 hours. This will mitigate the risk associated with next-day residual effects of DPH to some extent and is deemed acceptable.

Study 16135: A Bioavailability Trial of Naproxen Sodium and Diphenhydramine Hydrochloride under Fasting Conditions and Naproxen Sodium/ Diphenhydramine Hydrochloride Combination Product under Fasting and Fed Conditions (Study Period: Jan 23, 2012 – Mar 15, 2012)

Objective	To determine and compare the pharmacokinetic (PK) profile (specifically AUC and Cmax) of a single oral dose of currently marketed single ingredient products containing naproxen sodium (2 x 220 mg tablets) or diphenhydramine HCl (DPH HCl 2 x 25 mg tablets) relative to a single dose of naproxen sodium 440 mg/DPH HCl 50 mg combination product (2 x naproxen sodium 220 mg/DPH HCl 25 mg tablets) under fasting conditions. To determine and compare the PK profile (specifically AUC and Cmax) of a single dose of naproxen sodium 440 mg/DPH HCl 50 mg combination product (2 x naproxen sodium 220 mg/DPH HCl 25 mg tablets) under fasting and fed conditions.
Study Design	This was a Phase 1, randomized, open-label, four-way cross-over, single-center study conducted in healthy subjects. There were five visits to the study site (Screening Visit and Dosing Periods 1, 2, 3 and 4). Each dosing period consisted of Day 0, Day 1 and Day 2. Following a screening period of up to 14 days, eligible subjects were randomized to receive their first dose of investigational product in Period 1. Subjects were admitted to the clinic the day prior to dosing (Day 0), received their assigned dose of investigational product on Day 1 at approximately 8:00 AM and were discharged from the study site on Day 2, approximately 36 hours post-dose. There was a 7 day wash-out between dosing on Day 1 of each Dosing Period. Subjects were randomized to one of four randomization sequences ACBD, BADC, CDAB, DBCA, where: Treatment A = 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product under fasted conditions. Treatment B = 2 x Aleve (naproxen sodium 220 mg tablet) under fasted conditions. Treatment C = 2 x Allergy Relief (DPH HCl 25 mg tablet) under fasted condition. Treatment D = 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product under fed conditions (defined as consuming a standard high-fat, high-calorie breakfast within 30 minutes prior to investigational product administration).
Study Population	Thirty-two healthy adult subjects (15 male, 17 female) were randomized to receive study treatment and 27 subjects completed the study as planned. Subjects ranged from 20 to 55 years of age. Overall mean (SD) age was 36.8 (9.14) years, and mean (SD) weight, height and body mass index (BMI) were 74.3 (12.75) kg, 167.3 (12.34) cm, and 26.4 (2.49) kg/m2, respectively. Racial composition was 17 (53.1 %) White and 15 (46.9 %) Black or African American, and ethnicity was 15 (46.9%) Hispanic or Latino and 17 (53.1%) non-Hispanic or Non-Latino.
PK Assessments	Blood samples for plasma drug concentration measurements were collected prior to dosing (time 0) and 10, 20, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 24 and 36 hours post-dose. Primary PK variables were C_{max}, AUC_{0-t} and AUC_{0-inf} of naproxen and DPH.

Bioanalytical Methods

Analyte	Naproxen (µg/ml)	Diphenhydramine (ng/ml)
Method	LC-MS/MS	LC-MS/MS
Internal Standard	D_3-Naproxen	D_3-Diphenhydramine
LLOQ	0.50	0.50
Calibration Range	0.5, 1, 2.5, 5, 10, 50, 100, 200	0.5, 1, 2, 5, 10, 50, 100, 200

		QC	1.5, 16, 160	1.5, 20, 160
		Accuracy (%Actual)	96.7 – 105%	90.9 – 109%
		Precision (%CV)	3.5 – 8.0%	1.1 – 6.1%
	The bioanalytical methods are validated.			
Safety	Clinical laboratory tests, vital signs and adverse event (AE) reporting			

Results

1. There is no drug-drug interaction (DDI) for the combination product. The 90% CIs of the geometric mean ratio for naproxen C_{max} (87.9, 98.3), $AUC_{0\text{-}inf}$ (99.8, 105.2), and $AUC_{0\text{-}t}$ (98.7,102), following administration of naproxen sodium 440 mg/DPH HCl 50 mg vs. Aleve® 440 mg were contained within the equivalence range of 80% and 125%. The 90% CIs of the geometric mean ratio for DPH C_{max} (86.8, 106.4), $AUC_{0\text{-}inf}$ (97.1, 107.1), and $AUC_{0\text{-}t}$ (97.6, 107.1), following administration of naproxen sodium 440 mg/DPH HCl 50 mg vs. commercially available Allergy Relief 50 mg were contained within the equivalence range of 80% and 125%. The findings of no DDI were consistent with a literature study which was conducted in 30 healthy male and female subjects and demonstrated that a single-dose oral co-administration of 220 mg of naproxen sodium with 50 mg of DPH does not alter the PK of either naproxen or DPH (Toothaker RD, et al. Biopharm Drug Dispos. 2000 Sep;21(6):229-33).

2. Food (high-fat meal) had no effect on the overall exposure of naproxen or DPH in the combination product, however, there was a delay in the rate of absorption for naproxen with a lower (19%) C_{max} under fed state. The 90% CIs of the geometric mean ratio for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ of naproxen were (92.1, 97.0) and (95.2, 98.4), respectively, and for DPH, were (108.2, 119.6) and (107.6, 118.1), respectively, when comparing naproxen sodium 440 mg/DPH HCl 50 mg under fed state to fasted conditions. The 90% CI of the geometric mean ratio for C_{max} of naproxen was (76.1, 85.1), and for DPH, was (102.2, 125.4). The median of T_{max} for naproxen was delayed from 1.25 (range: 0.33 – 3.0) hrs under fasted condition to 3.0 (0.75 – 6.0) hrs under fed state. The T_{max} of DPH was less affected by the status of food intake, being 2.5 (1.0 – 4.0) hrs under fasted condition and 2.5 (1.25 – 6.0) hrs under fed state. C_{max} of DPH was 13% higher under fed state.

Table 1. Summary statistics of naproxen and DPH PK parameters

PK parameter (unit)	Treatment A (N=27)	Treatment B (N=27)	Treatment C (N=27)	Treatment D (N=27)
Naproxen				
C_{max} (µg/mL)	74.64 (10.370)	80.41 (11.487)		60.83 (11.130)
$AUC_{0\text{-}t}$ (µg*hr/mL)	913.2 (135.83)	909.1 (124.78)	N/A	882.4 (119.24)
$AUC_{0\text{-}inf}$ (µg*hr/mL)	1063 (156.9)	1060 (147.1)		980.7 (138.79)
t_{max} (h)	1.250	0.750		3.000
$t_{1/2}$ (h)	17.02 (3.828)	16.52 (2.563)		16.39 (2.941)
DPH				
C_{max} (ng/mL)	67.72 (27.125)		68.86 (22.446)	77.07 (34.987)
$AUC_{0\text{-}t}$ (ng*hr/mL)	613.9 (238.45)	N/A	598.2 (233.51)	685.3 (263.53)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	646.5 (239.62)		636.4 (257.55)	709.5 (267.03)
t_{max} (h)	2.500		1.750	2.500
$t_{1/2}$ (h)	10.96 (2.685)		10.85 (2.474)	10.80 (1.883)

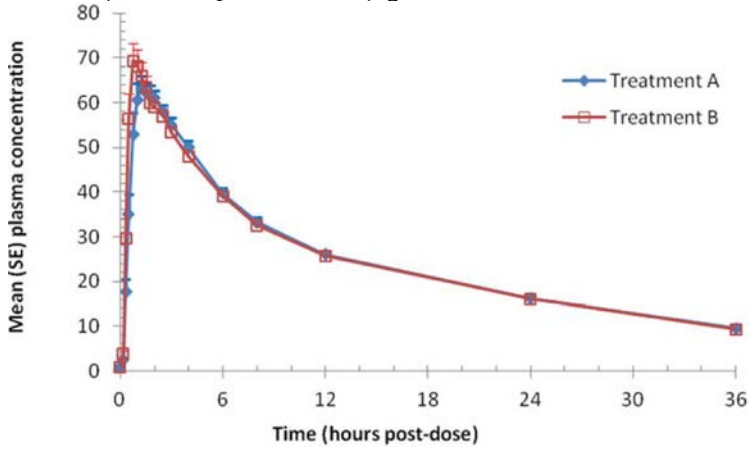
Table 2. Summary of bioequivalence analysis (C_{max}, AUC and T_{max})

PK	Statistic	Treatment A / B	Treatment A / C	Treatment D / A
Naproxen				
C_{max}	Estimated ratio	0.93	N/A	0.81
	90% CIs	87.9, 98.3		76.1, 85.1
$AUC_{0\text{-}inf}$	Estimated ratio	1.02	N/A	0.94
	90% CIs	99.8, 105.2		92.1, 97.0
$AUC_{0\text{-}t}$	Estimated ratio	1.00	N/A	0.97
	90% CIs	98.7, 102.0		95.2, 98.4
DPH				
C_{max}	Estimated ratio	N/A	0.96	1.13
	90% CIs		86.8, 106.4	102.2, 125.4
$AUC_{0\text{-}inf}$	Estimated ratio	N/A	1.02	1.14
	90% CIs		97.1, 107.1	108.2, 119.6
$AUC_{0\text{-}t}$	Estimated ratio	N/A	1.02	1.13
	90% CIs		97.6, 107.1	107.6, 118.1

Analyte	Ratio of t_{max} medians Treatment D / A	90% CIs
Naproxen	2.081	167.3, 275.2
DPH	1.118	86.6, 136.9

A: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fasted conditions
B: 2 x Aleve® (naproxen sodium 220 mg tablet) under fasted conditions
C: 2 x Allergy Relief® (DPH HCl 25 mg tablet) under fasted conditions
D: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fed conditions

Figure 2. Geometric mean (SE) plasma concentrations versus time. Upper panel: naproxen (µg/ml, Treatment A vs. Treatment B); Lower panel: DPH (ng/ml, Treatment A vs. Treatment C)



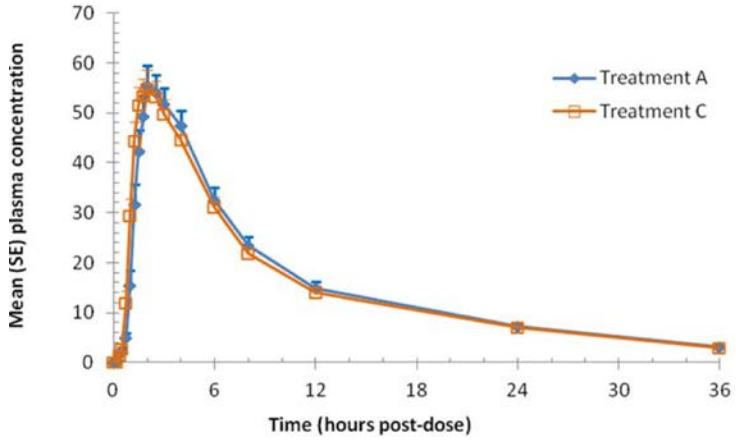


Figure 3. Geometric mean (SE) plasma naproxen concentrations (μg/mL) versus time: Treatment A versus Treatment D

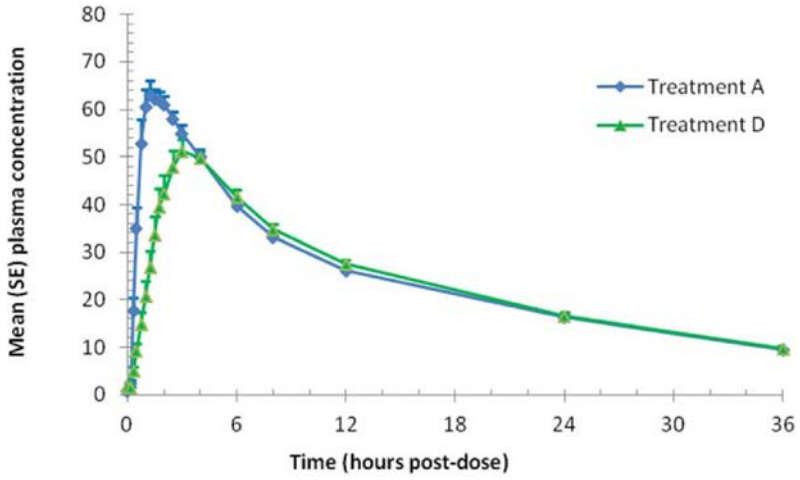
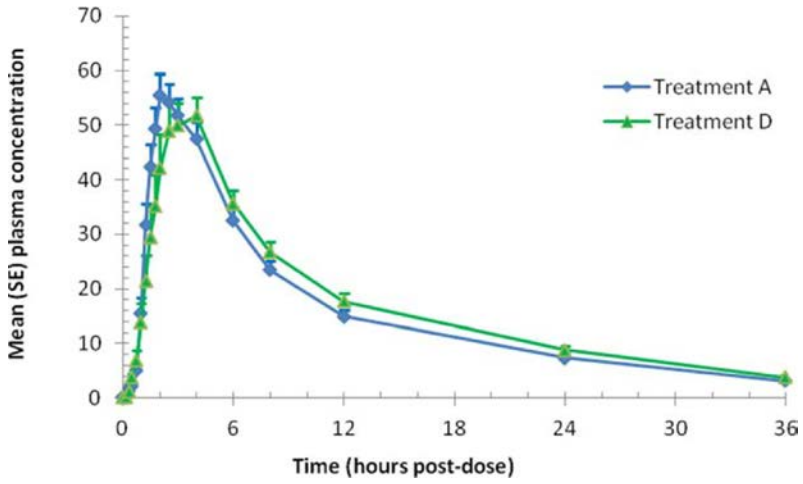


Figure 4. Geometric mean (SE) plasma DPH concentrations (ng/mL) versus time: Treatment A versus Treatment D

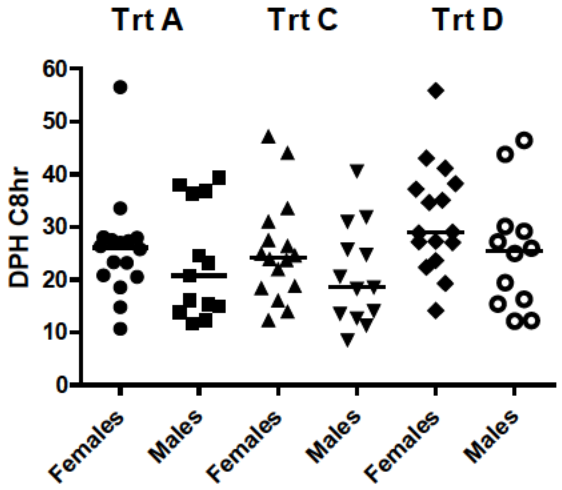


A: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fasted conditions
D: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fed conditions

3. Gender Difference in PK of DPH

Females appeared to have 14-30% higher DPH plasma concentrations than males at 8 hours post-dose (C_{8hr}, based on geometric mean values).

Figure 5. Plasma concentrations of DPH at 8 hours post-dose (C_{8hr}) grouped by gender for Treatments A, C and D. The horizontal bars represent medians.



A: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fasted conditions
C: 2 x Allergy Relief® (DPH HCl 25 mg tablet) under fasted conditions
D: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fed conditions

Table 3. Descriptive statistics of plasma concentrations of DPH at 8 hours post-dose (C_{8hr}) grouped by gender for Treatments A, C and D.

C8hr	Aleve PM (fasted)			DPH HCl 50 mg (fasted)			Aleve PM (fed)		
(ng/ml)	Females	Males	F/M	Females	Males	F/M	Females	Males	F/M
N	16	13		16	13		16	12	
Mean	25.75	23.31	1.10	25.49	20.87	1.22	31.49	25.24	1.25
SD	9.96	10.66		9.75	9.46		10.28	11.23	
CV%	39	46		38	45		33	45	
Geometric mean	24.21	21.17	1.14	23.88	18.97	1.26	29.92	23.06	1.30
Median	26.08	20.73	1.26	24.22	18.54	1.31	28.96	25.46	1.14
Min	10.69	11.68		12.28	8.53		14.15	12.13	
Max	56.52	39.30		47.16	40.60		55.88	46.44	

Safety Results	Overall, 29 (90.6 %) subjects experienced at least one treatment-emergent adverse event (TEAE) during the study. Fifteen (51.7%), 5 (16.7%), 16 (55.2%) and 14 (50.0%) subjects experienced at least one TEAE following administration of Treatment A, Treatment B, Treatment C and Treatment D, respectively. All AEs were considered mild in intensity and all AEs were considered resolved prior to discharge from the study or at follow-up visits. No subject discontinued study treatment because of an AE and no serious AEs (SAEs) were reported.

	The most common TEAE was somnolence, reported by 23 subjects who received DPH (37.9-48.3%), either as the combination product (Treatment A, Treatment D) or as the single-ingredient product (Treatment C). In general, somnolence onset occurred during the 1-3 hour post-dose period and duration for each subject varied from 1 to 10 hours. Median plasma DPH T_{max} for all subjects ranged from 1.75-2.5 hours, coinciding with the period of somnolence onset. However, there was no correlation between the duration of somnolence and C_{8hr} of DPH. For example, Subject 140011026 had the highest C_{8hr} of DPH in each treatment period, while she only reported somnolence in Treatment periods A and D. The somnolence only lasted for 0.65 hrs and 2.83 hrs in Treatment periods A and D, respectively, much shorter than the duration observed in a number of other subjects who had lower C_{8hr} of DPH.
Conclusions	There was no drug-drug interaction when naproxen sodium is combined with DPH HCl in the combination product. There was no food effect on the extent of absorption of naproxen or DPH in the combination product, however, there is a delay in the rate of absorption for naproxen under fed state with a lower peak plasma concentration. Food intake increased the peak plasma concentration of DPH slightly. Females appeared to have 14-30% higher DPH plasma concentrations than males at 8 hours post-dose (based on geometric mean values). The clinical significance of such difference is unknown.

Comparison of Diphenhydramine (DPH) plasma concentrations between Aleve PM and other DPH-containing products

One of the side effects of DPH is drowsiness/somnolence, which may impair driving skills in the next morning. Several DPH-containing products have been approved and used by a large population for many years. In order to make sure that the safety profile of Aleve PM is comparable to the other DPH-containing products, cross-study comparisons of the DPH plasma levels after 8-12 hours of administration is conducted, assuming that DPH concentrations around the time of waking are related to drowsiness and impairment of driving ability. A list of some approved DPH-containing products was provided by DNCE medical officers and is shown in the table below.

Product Name	spl ID*	Generic Name	Market category	PK Data	Directions for Dosing
Advil PM	86534 84705	IBUPROFEN (200 mg), DIPHENHYDRAMINE CITRATE (38 mg)	NDA (20,4 caplet package)	Yes	2 caplets at bedtime, not to exceed 2 caplets in 24 hrs
Advil PM	24159	IBUPROFEN (200 mg), DIPHENHYDRAMINE HYDROCHLORIDE (25 mg)	NDA (32 capsule package)	Yes	2 capsules at bedtime, not to exceed 2 capsules in 24 hrs
Motrin PM	15110	IBUPROFEN (200 mg), DIPHENHYDRAMINE CITRATE (38 mg)	ANDA (80 caplet package)	Yes	2 caplets at bedtime, not to exceed 2 caplets in 24 hours
Tylenol PM Extra Strength	16354 16283 22388	ACETAMINOPHEN (500 mg), DIPHENHYDRAMINE HYDROCHLORIDE (25 mg)	OTC monograph not final (100 caplet package) (80 gelcap package) (100 geltab package)	No	2 caplets at bedtime, not to exceed 2 caplets in 24 hrs
Excedrin PM	18184 18191	ACETAMINOPHEN (500 mg), DIPHENHYDRAMINE CITRATE (38 mg)	OTC monograph final (100 tablet package) and (50 caplet package)	No	2 tablets at bedtime

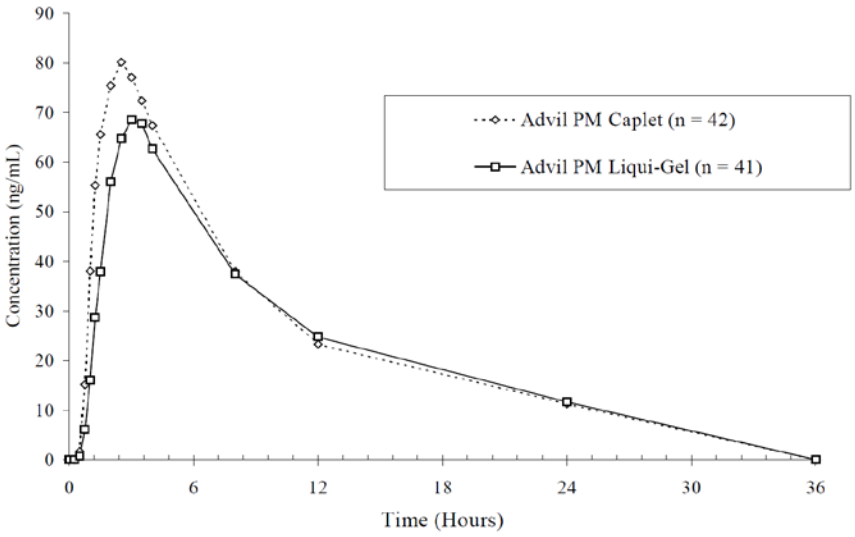
*SPL: Structured Product Labeling

Overview of bioequivalence study AE-00-10 ("A randomized, single-dose, two-way crossover bioequivalence study comparing Advil® PM caplets to Advil® PM Liqui-Gel")

Data for this comparison were obtained from NDA 21-393 and NDA 21-394.

- Study AE-00-10 was conducted to determine if the caplet formulation of Advil® PM is bioequivalent to the liquid-gel formulation, when administered under fasted conditions.
- The study was a single-center, randomized (stratified by gender), open-label, single-dose, two-way crossover bioequivalence trial in 42 healthy male and female subjects (21 of each gender), aged 21-45 years. All subjects completed the study except for one male.
- Treatment A: Two Advil® PM Caplets, each containing ibuprofen 200 mg and diphenhydramine citrate 38 mg
- Treatment B: Two Advil® PM Liqui-Gels, each containing ibuprofen 200 mg and diphenhydramine HCl 25 mg

Figure 6. Mean DPH Plasma Concentrations versus Time

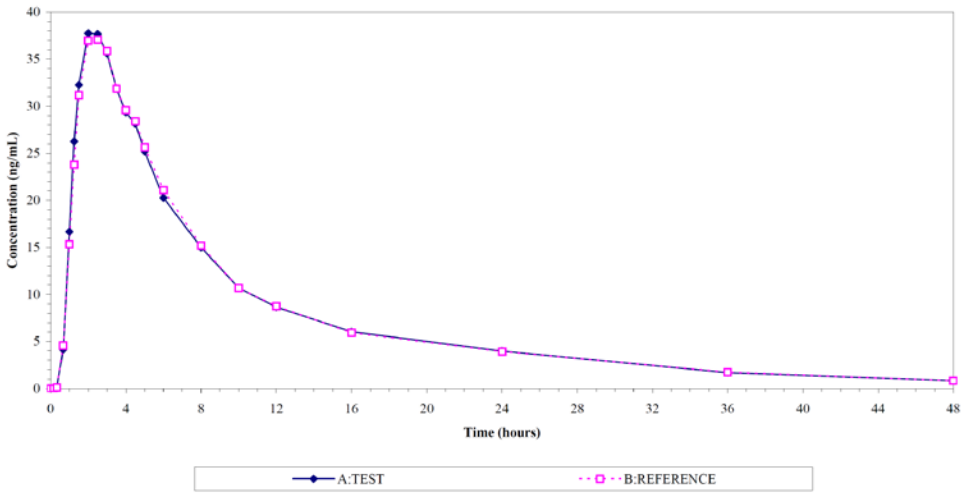


Overview of bioequivalence study R06-0740 ("A Relative Bioavailability Study of Ibuprofen/Diphenhydramine Citrate (200 mg/38 mg) Tablets vs. Caplets under Fasting Conditions")

Data for this comparison were obtained from ANDA 79-113.

This was a single dose, randomized, two-period, two-treatment, two-sequence crossover study. This study compared the relative bioavailability (rate and extent of absorption) of the test product, ibuprofen/diphenhydramine citrate (200 mg/38 mg) tablet by Perrigo R&D company, with that of the reference product, Advil® PM caplets by Wyeth Consumer Healthcare, following single oral doses (1 x 200 mg/38 mg tablet or caplet) in healthy adult males (N=19) and females (N=25) administered under fasted conditions.

Figure 7. DPH Mean Plasma Concentrations (0-48 hours)



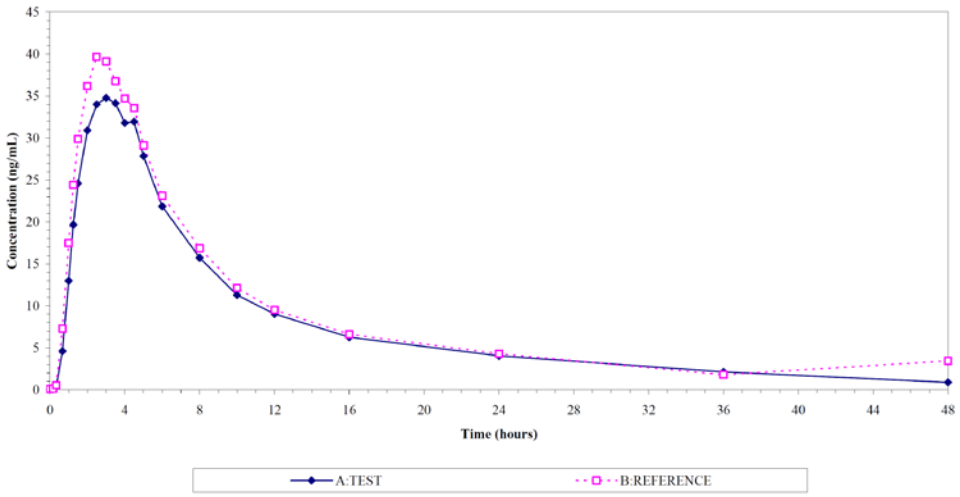
Overview of bioequivalence study R06-0741 ("A Relative Bioavailability Study of Ibuprofen/Diphenhydramine Citrate (200 mg/38 mg) Tablets vs. Caplets under Non-Fasting Conditions")

Data for this comparison were obtained from ANDA 79-113.

This was a single dose, randomized, two-period, two-treatment, two-sequence crossover study conducted under non-fasting conditions.

This study compared the relative bioavailability (rate and extent of absorption) of ibuprofen/diphenhydramine citrate (200 mg/38 mg) tablets by Perrigo R&D Company (test) with that of Advil® PM caplets by Wyeth Consumer Healthcare (reference), following a single oral dose (1 x 200 mg/38 mg tablet or caplet) in healthy adult males (N=15) and females (N=29).

Figure 8. DPH Mean Plasma Concentrations (0-48 hours)



PK results are summarized as mean ± SD (range) in the tables below.

Product name (Fasted condition)	DPH Dose	Concentration at 8 h (ng/ml)	Concentration at 12 h (ng/ml)
Aleve PM	2x25 mg DPH HCl	24.7 ± 10.2 (10.7 - 56.5)	15.7 ± 7.3 (6.3 - 39.1)
Advil PM Liqui-gel	2x25 mg DPH HCl	37.4 ± 12.9 (17.8 - 67.5)	24.8 ± 11.0 (12.0 - 61.6)
Advil PM Caplets	2x38 mg DPH Citrate	37.9 ± 16.5 (16.4 - 99.3)	23.3 ± 9.4 (11.1 - 55.4)
Advil PM Caplets	1x38 mg DPH Citrate	15.2 ± 6.1 (6.1 - 31.4)	8.7 ± 4.0 (2.6 - 20.7)
Motrin PM	1x38 mg DPH Citrate	15.0 ± 6.3 (4.9 - 30.4)	8.7 ± 4.1 (2.3 - 18.5)

Note: DPH citrate 38 mg contains the same amount of free base DPH as DPH HCl 25 mg.

Product name (Fed state)	DPH Dose	Concentration at 8 h (ng/ml)	Concentration at 12 h (ng/ml)
Aleve PM	2x25 mg DPH HCl	28.8 ± 11.0 (12.1 - 55.9)	19.5 ± 8.7 (7.4 - 43.3)
Advil PM Caplets	1x38 mg DPH Citrate	16.9 ± 6.7 (6.7 -39.1)	9.5 ± 4.7 (3.0 - 26.6)
Motrin PM	1x38 mg DPH Citrate	15.7 ± 6.8 (6.4 - 43.9)	9.0 ± 4.8 (2.6 - 28.9)

Note: DPH citrate 38 mg contains the same amount of free base DPH as DPH HCl 25 mg.

Based on DPH plasma levels measured at 8 hours and 12 hours after administration of different DPH-containing products, it is concluded that Aleve PM does not have higher DPH concentrations in comparison to the other approved products. These findings suggest that Aleve PM is unlikely to have more severe side effects than the approved DPH-containing products.

Xinning Yang, Ph.D., Bilal AbuAsal, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D. Ph.D._____

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

/s/

XINNING YANG
12/20/2013

BILAL S ABU ASAL
12/20/2013

YUXIN MEN
12/20/2013