

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205352Orig1s000

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

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 H₁-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-inf} , and AUC_{0-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.

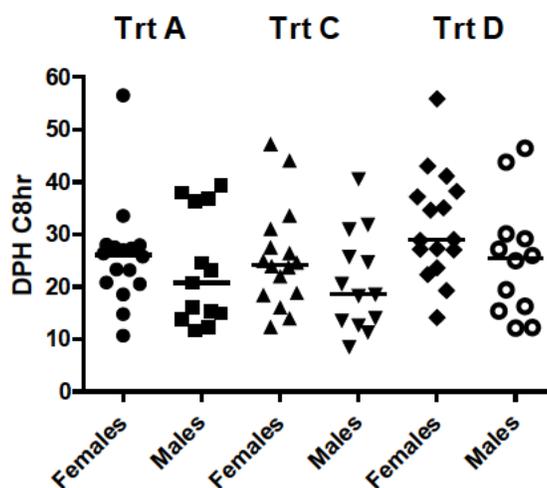
Food (high-fat meal) had no effect on the overall exposure (AUC) of naproxen or DPH in the combination product. Food intake decreased naproxen C_{max} by 19% and delayed its T_{max} to 3.0 (range: 0.75 – 6.0) hrs compared to 1.25 (range: 0.33 – 3.0) hrs under fasted conditions. In the proposed labeling, 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 Pharmacol 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/mL) 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	<p>To determine and compare the pharmacokinetic (PK) profile (specifically AUC and C_{max}) 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.</p> <p>To determine and compare the PK profile (specifically AUC and C_{max}) 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.</p>																	
Study Design	<p>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.</p> <p>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).</p>																	
Study Population	<p>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.</p>																	
PK Assessments	<p>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.</p>																	
Bioanalytical Methods		<table border="1"> <tr> <td>Analyte</td> <td>Naproxen (µg/ml)</td> <td>Diphenhydramine (ng/ml)</td> </tr> <tr> <td>Method</td> <td>LC-MS/MS</td> <td>LC-MS/MS</td> </tr> <tr> <td>Internal Standard</td> <td>D₃-Naproxen</td> <td>D₃-Diphenhydramine</td> </tr> <tr> <td>LLOQ</td> <td>0.50</td> <td>0.50</td> </tr> <tr> <td>Calibration Range</td> <td>0.5, 1, 2.5, 5, 10, 50, 100, 200</td> <td>0.5, 1, 2, 5, 10, 50, 100, 200</td> </tr> </table>	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	
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		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-inf} (99.8, 105.2), and AUC_{0-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-inf} (97.1, 107.1), and AUC_{0-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-inf} and AUC_{0-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

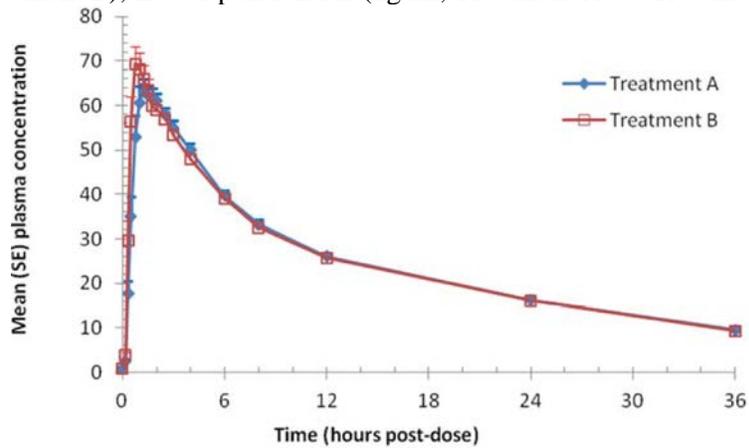
PK parameter (unit)	Treatment A (N=27)	Treatment B (N=27)	Treatment C (N=27)	Treatment D (N=27)
Naproxen				
C_{max} (µg/mL)	74.64 (10.370)	80.41 (11.487)		60.83 (11.130)
AUC_{0-t} (µg*hr/mL)	913.2 (135.83)	909.1 (124.78)	N/A	882.4 (119.24)
AUC_{0-inf} (µg*hr/mL)	1063 (156.9)	1060 (147.1)		980.7 (138.79)
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-t} (ng*hr/mL)	613.9 (238.45)	N/A	598.2 (233.51)	685.3 (263.53)
AUC_{0-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-inf}	Estimated ratio	1.02	N/A	0.94
	90% CIs	99.8, 105.2		92.1, 97.0
AUC _{0-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-inf}	Estimated ratio	N/A	1.02	1.14
	90% CIs		97.1, 107.1	108.2, 119.6
AUC _{0-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		90% CIs	
	Treatment D / A			
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 ($\mu\text{g/ml}$, Treatment A vs. Treatment B); Lower panel: DPH (ng/ml, Treatment A vs. Treatment C)



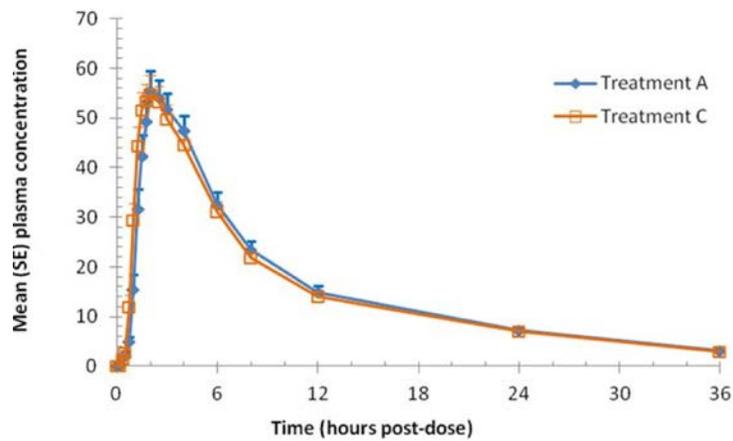


Figure 3. Geometric mean (SE) plasma naproxen concentrations ($\mu\text{g/mL}$) versus time: Treatment A versus Treatment D

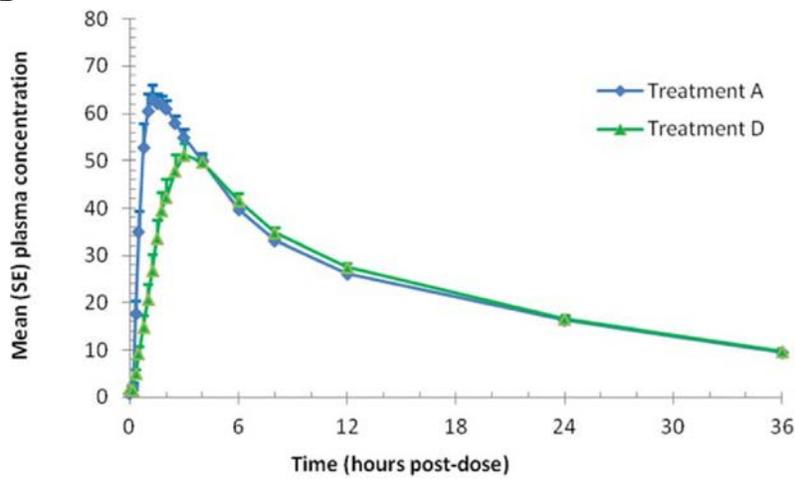
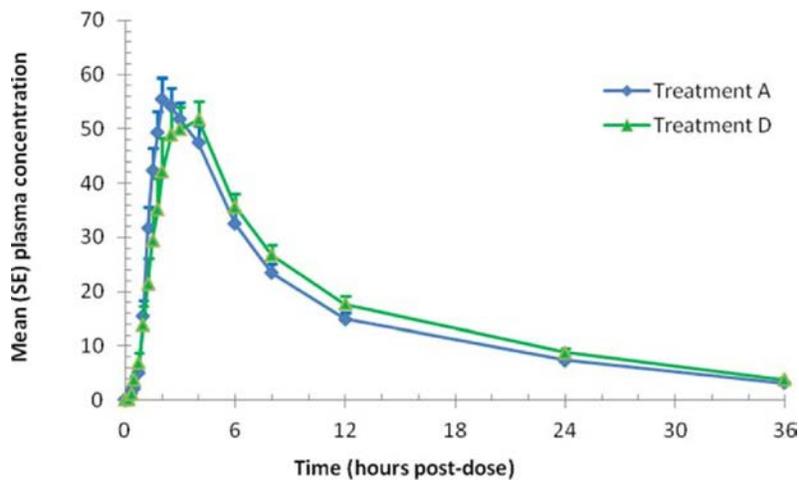


Figure 4. Geometric mean (SE) plasma DPH concentrations (ng/mL) versus time: Treatment A versus Treatment D

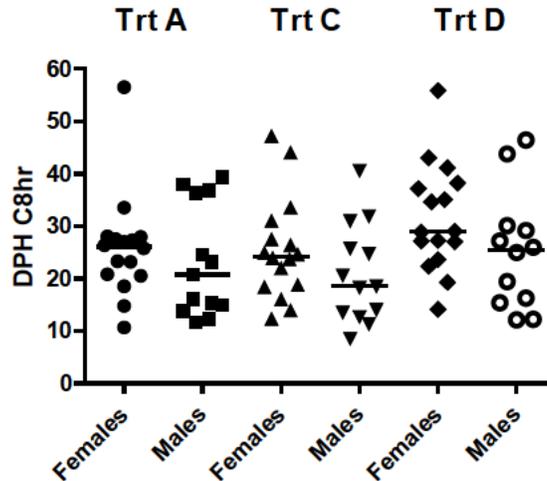


A: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fasted conditions
 D: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fed conditions

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 (ng/ml)	Aleve PM (fasted)			DPH HCl 50 mg (fasted)			Aleve PM (fed)		
	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.

	<p>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.</p>
<p>Conclusions</p>	<p>There was no drug-drug interaction when naproxen sodium is combined with DPH HCl in the combination product.</p> <p>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.</p> <p>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.</p>

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

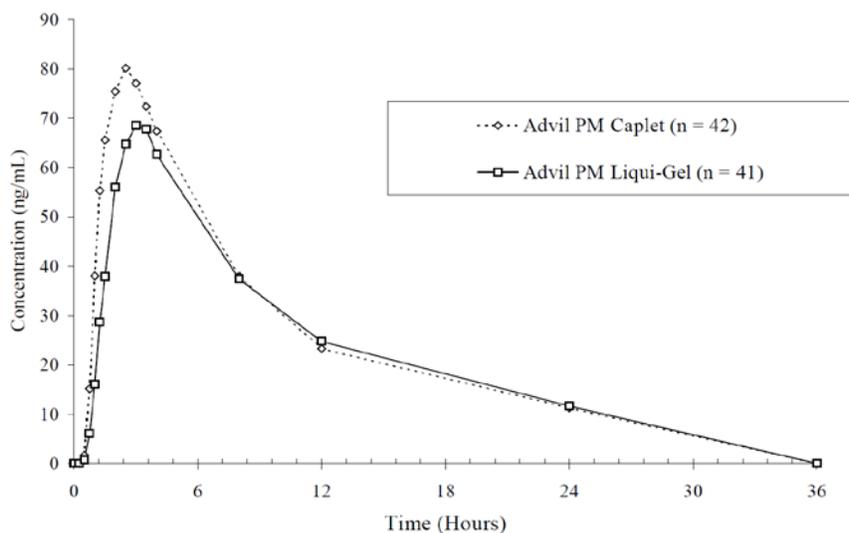
*SPL: Structured Product Labeling

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

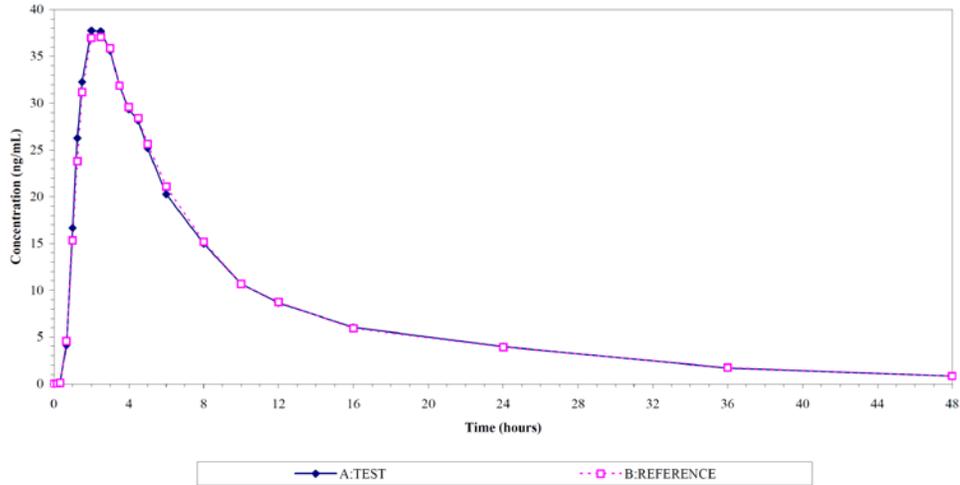


Overview of bioequivalence study R06-0740 (“A Relative Bioavailability Study of Ibuprofen/Diphenhydramine Citrate (200 mg/38 mg) Tablets vs. Caplets under Fasting Conditions”)

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)



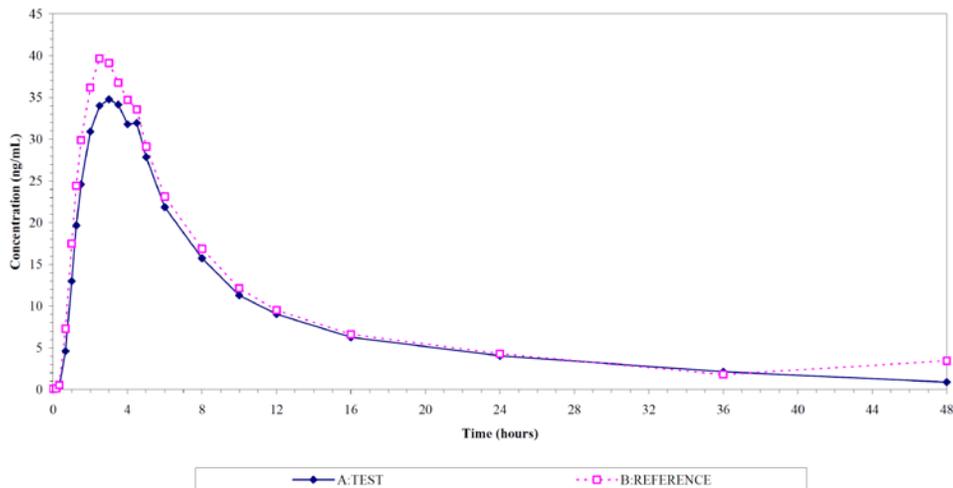
Overview of bioequivalence study R06-0741 (“A Relative Bioavailability Study of Ibuprofen/Diphenhydramine Citrate (200 mg/38 mg) Tablets vs. Caplets under Non-Fasting Conditions”)

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 \pm 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 \pm 10.2 (10.7 - 56.5)	15.7 \pm 7.3 (6.3 - 39.1)
Advil PM Liqui-gel	2x25 mg DPH HCl	37.4 \pm 12.9 (17.8 - 67.5)	24.8 \pm 11.0 (12.0 - 61.6)
Advil PM Caplets	2x38 mg DPH Citrate	37.9 \pm 16.5 (16.4 - 99.3)	23.3 \pm 9.4 (11.1 - 55.4)
Advil PM Caplets	1x38 mg DPH Citrate	15.2 \pm 6.1 (6.1 - 31.4)	8.7 \pm 4.0 (2.6 - 20.7)
Motrin PM	1x38 mg DPH Citrate	15.0 \pm 6.3 (4.9 - 30.4)	8.7 \pm 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 \pm 11.0 (12.1 - 55.9)	19.5 \pm 8.7 (7.4 - 43.3)
Advil PM Caplets	1x38 mg DPH Citrate	16.9 \pm 6.7 (6.7 - 39.1)	9.5 \pm 4.7 (3.0 - 26.6)
Motrin PM	1x38 mg DPH Citrate	15.7 \pm 6.8 (6.4 - 43.9)	9.0 \pm 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. _____

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/s/

XINNING YANG
12/20/2013

BILAL S ABU ASAL
12/20/2013

YUXIN MEN
12/20/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205352	Reviewer: Minerva Hughes, Ph.D.	
Submission Date:	20 March 2013		
Division:	Division of Nonprescription Clinical Evaluation	Team Leader: Angelica Dorantes, Ph.D.	
		Acting Supervisor: Richard Lostritto, Ph.D.	
Sponsor:	Bayer Healthcare	Secondary Reviewer: Team Leader	
Trade Name:	(proposed name Aleve PM)	Date Assigned:	15 April 2013
		GRMP Date:	14 December 2013
		PDUFA Date:	20 January 14
Generic Name:	Naproxen Sodium/diphenhydramine	Date of Review:	6 December 2013
Indication:	Relief of occasional sleeplessness associated with minor aches and pains	Type of Submission: 505(b)(2) Original NDA	
Formulation/strengths	Tablet (FDC)/ 220 mg naproxen and 25 mg diphenhydramine		
Route of Administration	Oral		
Biopharmaceutics Review Focus: Dissolution method and acceptance criteria			
SUMMARY			
<p>Submission: NDA 205-352 was submitted in accordance with Section 505(b)(2) of the FDC Act for the use of naproxen sodium and diphenhydramine (DPH) as a fixed dose combination to relieve occasional sleeplessness associated with minor aches and pains. Naproxen sodium has been marketed as an over-the-counter (OTC) product in the US since 1994 and is currently approved for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, and backache; for the minor pain of arthritis; for the pain of menstrual cramps; and for the reduction of fever. Naproxen sodium is approved in the US at OTC doses of 220 mg and 440 mg for use by adults and children at least 12 years of age or older. DPH, under the brand name Benadryl, received marketing approval in the US in 1946 for use as a prescription antihistamine and was later monographed in 1982 for use as a sleep aid at a dose of 50 mg (21 CFR 338).</p> <p>There are several OTC analgesic + nighttime sleep-aid combination products available in the US indicated for pain accompanied by sleeplessness. However, there are no OTC analgesic + nighttime sleep-aid combination products available in the US that combined naproxen sodium with DPH.</p> <p>Review: The biopharmaceutics review topics presented in this NDA included the following:</p> <ul style="list-style-type: none"> - Dissolution method and acceptance criteria - Dissolution data for the over-encapsulated tablets used in the clinical studies - Dissolution stability <p>The clinical trial drug product that was used in the pivotal studies is the to-be-marketed drug product (same tablet but over-encapsulated). The comparative dissolution data between the over-encapsulated and free tablet demonstrated comparable performance and no additional bridging studies are warranted to support approval. A dissolution test was included in the specifications of the drug product as an important quality measure of product bioavailability. The adequacy of the proposed dissolution method was supported by the provided dissolution method report, which included the necessary method</p>			

development and dissolution data for FDA's review.

RECOMMENDATION:

Based on the review of the provided dissolution data, the following dissolution method and acceptance criteria for naproxen sodium and DPH tablets are acceptable for routine quality control.

Dissolution Parameter	Criteria
Appartus	USP 2
Medium	900 mL, de-aerated 0.1M sodium phosphate buffer, pH 7.4
Paddle Rotation Speed	75 rpm
Sampling Time/	0, 10, 15, 20, 30, 45, 60 (profiles)
Analytical	HPLC
Acceptance Criteria	Naproxen sodium Q = $\frac{(b)}{(4)}$ % at 30 min Diphenhydramine hydrochloride Q = $\frac{(b)}{(4)}$ % at 30 min

Because incomplete dissolution data were collected during the stability program, it should be noted that the Applicant has committed to collecting complete dissolution profile data on the future stability pulls. The dissolution acceptance criterion recommended for approval, however, is supported by the performance of at least 12 months' aged registration stability lots.

There are no outstanding issues or post-marketing commitments to note in the action letter.

From the perspective of Biopharmaceutics, NDA 205352 for Naproxen sodium/ Diphenhydramine HCl tablets is recommended for approval.

Minerva Hughes, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

1.0 GENERAL INFORMATION

1.1 General

Bayer HealthCare Consumer Care (Bayer) submits this new drug application (NDA) for naproxen sodium 220 mg + diphenhydramine hydrochloride (DPH) 25 mg as an over-the-counter (OTC), two-tablet oral dose under the proposed trade name Aleve® PM. The proposed indication is for the relief of occasional sleeplessness associated with minor aches and pains.

1.2 Drug Substance Summary

The drug substance, naproxen sodium, is a well-established and effective nonsteroidal anti-inflammatory drug (NSAID) approved for Over-The-Counter (OTC) use. The sodium salt possesses relatively good solubility in water when compared to the anion. The anionic molecule, naproxen, has been described as a propionic acid derivative with analgesic and antipyretic properties. The mechanism of action of naproxen and other NSAIDs has been associated with prostaglandin synthetase inhibition.

The drug substance, diphenhydramine, is a well-established OTC active ingredient. DPH is sedating and belongs to the monoethanolamine group of antihistamines. It is available in two forms, the citrate and the hydrochloride (HCl) salts. The HCl salt is used in this NDA and was selected based on in vitro dissolution performance. Specifications for both salts are provided in the USP monographs.

1.3 Drug Product Summary

The proposed drug product is a fixed-dose combination film-coated tablet. Two strengths were used in phase 3 studies, however, only the 220/25 mg (Naproxen/DPH) combination is proposed for marketing.

The drug product is manufactured  (b) (4)

The composition information is provided in the following table.

Table 8: Final Composition of the Naproxen Sodium/Diphenhydramine HCl 220/25mg and 220/50 mg Coated Caplets

Composition	Function	Formulation	
		220/25	220/50
(b) (4)		Amount, mg	Amount, mg
Naproxen Sodium	Drug Substance	220.0	220.0
Diphenhydramine HCl	Drug Substance	25.0	50.0
Microcrystalline Cellulose	(b) (4)		
Povidone			
Purified Water			
Talc			
Magnesium Stearate			
<i>Total</i> (b) (4) <i>Weight:</i>			
(b) (4)			
Hypromellose 2910	(b) (4)		
Titanium Dioxide			
FD&C Blue #2 Aluminum Lake			
Polyethylene Glycol 8000			
(b) (4)			
Carnauba Wax	(b) (4)		
<i>Total</i> (b) (4) <i>Weight:</i>		391.4	416.8
(b) (4)			

The formulation used in the clinical and PK studies is the to-be-marketed formulation. The tablets, however, were over-encapsulated (b) (4) for use in the clinical efficacy trials.

Reviewer’s Comment: The Applicant was requested to provide comparative dissolution profile data for the over-encapsulated tablets used in clinical studies compared with the free tablet to verify that encapsulation did not significantly affect product dissolution. These data are discussed in Section 2.3.

1.4 Biopharmaceutics Review Focus

This biopharmaceutics review evaluates the acceptability of the proposed dissolution method and acceptance criteria for product quality control at release and on stability.

2.0 BIOPHARMACEUTICS REVIEW TOPICS

2.1 Dissolution Method

The proposed dissolution method and acceptance criteria are as follow.

Parameter	Criterion
Appartus	USP 2
Medium	900 mL, de-aerated 0.1M sodium phosphate buffer, pH 7.4
Paddle Rotation Speed	75 rpm
Sampling Time/ Acceptance Criterion	0, 10, 15, 20, 30, 45, 60 (profiles) Naproxen sodium Q = $\frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ min Diphenhydramine hydrochloride Q = $\frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ min
Analytical	HPLC

2.1.1 Method Development/Justification Information

Drug Solubility/Medium Considerations (Report 3.2.P.2.2)

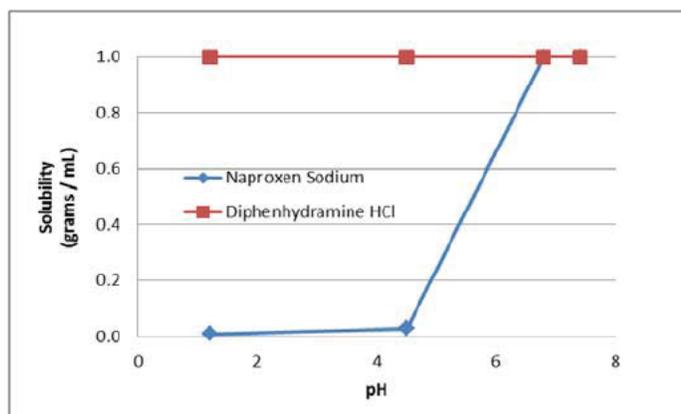
The drug substance solubility under saturating conditions across the physiological pH range is illustrated in the following table and figure.

	Naproxen Sodium		Diphenhydramine HCl	
	25°C	37°C	25°C	37°C
Concentration in Dissolution Test	-----	220 mg/900 mL (0.244 mg/mL)	-----	25 mg/900 mL (0.0278 mg/mL)
Sink Conditions (3 x Dissolution Conc.)	-----	0.732 mg/mL	-----	0.0834 mg/mL
pH 7.4	Freely Soluble*	Freely Soluble*	Freely Soluble*	Freely Soluble*
pH 6.8	Freely Soluble*	Freely Soluble*	Freely Soluble*	Freely Soluble*
pH 4.5	< 0.1 mg/mL**	< 0.1 mg/mL **	Freely Soluble*	Freely Soluble*
pH 1.2	0.01 mg/mL	< 0.03 mg/mL**	Freely Soluble*	Freely Soluble*

* Freely soluble is defined as greater than 1 gram in 10 mL.

** Based on Bayer internal data and the results obtained during this study

Figure 1 Plot of Solubility verses pH of API's at 37°C



Given its pKa of 4.2, naproxen sodium at a pH of 1.2 exists as a neutral compound, which is practically insoluble in water. (b) (4)

The Applicant notes that the USP monograph for naproxen sodium tablets defines pH 7.4 for the dissolution medium, and a pH consistent with the analytical method was preferred.

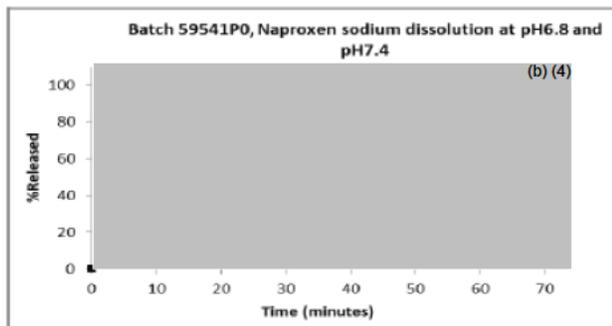


Figure 3: Naproxen Sodium Dissolution at pH 6.8 and 7.4 (Batch 59541P0)

Note: Figure legends retained as included in the submission. The dissolution study was performed using a USP 2 apparatus at 75 rpm.

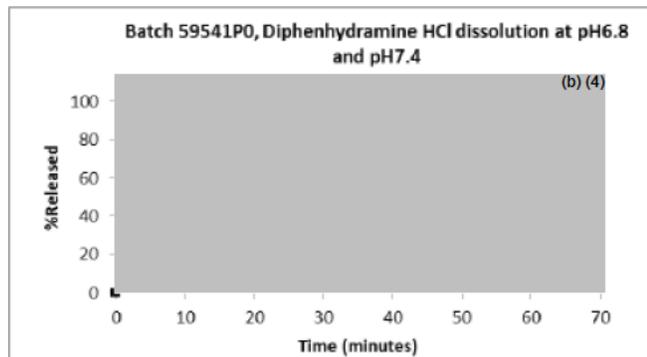


Figure 4: Diphenhydramine HCl Dissolution at pH 6.8 and 7.4 (Batch 59541P0)

Note: Figure legends retained as included in the submission. The dissolution study was performed using a USP 2 apparatus at 75 rpm.

A pH 7.4 dissolution medium was selected as optimal because the pH aligned with the USP monograph for naproxen sodium. A standard volume of 900 mL was used.

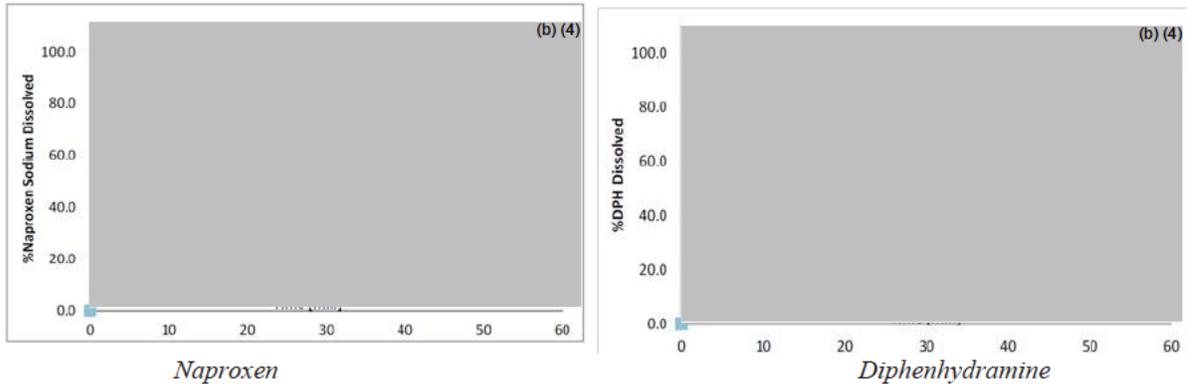
Reviewer's Assessment: Satisfactory. The Applicant reasonably investigated various buffer systems to select optimal conditions for the product. This Reviewer agrees that there is

minimal difference between pH 7.4 and pH 6.8 and since pH 7.4 is better suited, or at least recommended by USP, for the HPLC analytical method, pH 7.4 is acceptable.

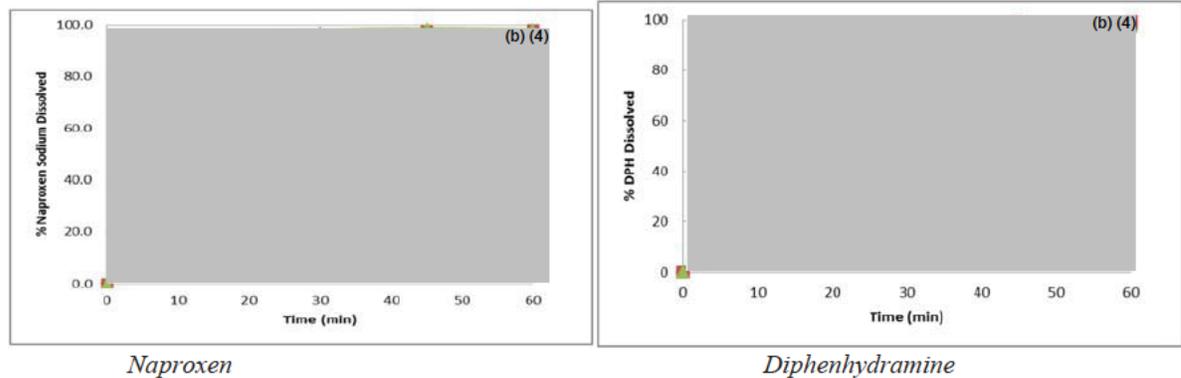
Apparatus/Agitation Speed

For this series of experiments, profile sampling was performed at 10, 15, 20, 30, 45 and 60 minutes using 900 mL of deaerated 0.1 M sodium phosphate buffer (pH 7.4). Apparatus 1 (baskets) was evaluated at 75, 100 and 125 rpm, and Apparatus 2 (paddles) at 50, 75 and 100 rpm. HPLC was used for quantitative analysis. These dissolution studies used registration Lot 6662 after 12 months storage.

Effect of Apparatus Type on Mean Dissolution



Effect of Paddle Speed on Mean Dissolution



Based on the observed results, the Applicant concluded that Apparatus 2 (Paddles) at 75 rpm is optimal for the proposed product. Even though the USP method for naproxen sodium tablets calls for 50 rpm, [REDACTED] (b) (4) the paddle method at 75 rpm using the pH 7.4 medium was selected as optimal.

Reviewer's Assessment: Satisfactory. This Reviewer notes that the Applicant favored the USP 2 apparatus compared with USP 1 [REDACTED] (b) (4)

(b) (4)

Analytical Method

An HPLC method was developed for naproxen and DPH analysis. The method was validated with respect to the following.

- Specificity
- Linearity
- Recovery/Accuracy
- Range
- Precision including
- Repeatability
- Intermediate precision
- Solution Stability
- Robustness

During the long term stability testing, however, it was found necessary to further modify the method procedures to,

- 1) improve the robustness of the assay sample preparation to minimize sporadic assay results, especially for diphenhydramine HCl.
- 2) improve HPLC column lifetime (b) (4)
- 3) improve column lifetime for assay analysis (b) (4)
- 4) improve column lifetime for impurities / degradation products analysis by (b) (4)
- 5) (b) (4)
- 6) reduce the use of impurity reference materials for routine analyses.

Reviewer's Evaluation: *The acceptability of the analytical method validation and implemented changes during development will be addressed by the assigned CMC Reviewer. (b) (4). From the Biopharmaceutics perspective, the drug substance appears stable under the dissolution testing conditions.*

Studies Completed to Evaluate the Method's Discriminating Ability

The following table summarizes the list of manufacturing variables that could impact dissolution and the experiments, if any, that were performed to evaluate that parameter.

Potential Changes	Impacting Attributes	Causative Factor	Inference	Experiment to be Performed
API	(b) (4)			
Formulation				
Process				

Potential Changes	Impacting Attributes	Causative Factor	Inference	Experiment to be Performed
	(b) (4)			

The mean dissolution results for the different studies are summarized in the following table.

(b) (4)



(b) (4)



Naproxen sodium, which has a (b) (4), is present at over (b) (4)% of the tablet weight and therefore significantly influences the (b) (4). The mechanism of tablet release is by (b) (4).

Reviewer's Evaluation: Satisfactory. *The Applicant's studies evaluating the discriminating ability of the method provided a good understanding of the method's utility. Early development studies (as summarized in the experimental summary table above) showed that the method could effectively distinguish between different salts of DPH.* (b) (4)

(b) (4)
In addition to the drug substance form, (b) (4) was important for product quality. The dissolution rate for tablets (b) (4)

(b) (4) dissolved significantly faster than the target formulation. It is noted, however, that dissolution is only impacted at this extreme and no effect was observed at (b) (4). Overall, the dissolution method was appropriately developed and evaluated to understand its utility for product quality control.

2.2 Dissolution Acceptance Limits/ Product Stability

The Applicant noted that based on ICH Q6A, single-point measurements are normally considered to be suitable for immediate-release dosage. Dissolution profiles suggested a (b) (4) minute timepoint was necessary for > (b) (4)% dissolution to occur, especially for Diphenhydramine HCl. Therefore, the Applicant proposed an acceptance criterion of $Q = (b) (4)\%$ at (b) (4) minutes for both naproxen and DPH.

Stability data included only single-point dissolution at (b) (4) minutes, with mean dissolution of essentially (b) (4)% through 12 months storage.

Reviewer's Evaluation: *The dissolution method development report included complete dissolution profile data for clinical and registration stability lots. However, the stability data reported only data at (b) (4) minutes. After an information request for dissolution profile data on stability, the Applicant clarified that the dissolution profile data in the method development report were obtained from registration lots after 12 months of storage. If the clinical samples were tested at the same time, these samples are >24 months old. The Applicant also committed to collecting complete dissolution profiles on the remaining stability pulls. This Reviewer evaluated the dissolution profile data collected during product development as well as from 12 month old batches and applied FDA's standard for defining dissolution acceptance limits for immediate released products – time point where mean dissolution > (b) (4)% occurs (representative raw data are appended to this review). Using this approach, the Applicant's proposed acceptance criterion of $Q = (b) (4)\%$ at (b) (4) minutes, though improved from (b) (4) minutes, is (b) (4). This Reviewer recommended an acceptance criterion of $Q = (b) (4)\%$ at 30 minutes, which the Applicant agreed to in the 1 October 2013 NDA amendment. This Reviewer also considered final sampling at 20 minutes; however, the Reviewer's calculated RSD for some lots was > (b) (4)% and with this variability, the dissolution method appeared most suitable for 30 minute sampling.*

Further, because the dissolution profile data were relatively consistent among the various lots, and recognizing the formulation attributes and risk factors for dissolution changes on stability based on this NDA and FDA's prior knowledge of naproxen and DPH products, this Reviewer found no significant objections to applying ICH's criteria for granting a 24 month expiry based on 12 months of data, despite the limited 30 minute dissolution data available. As previously mentioned, the Applicant commits to collecting the 30 minute dissolution data for the remaining stability pulls in the stability protocol. A final determination of the product's shelf life is deferred to CMC, however.

2.3 Formulation Changes During Development and CFR BA Requirement

Based on feedback from a Pre-IND meeting with the FDA, it was decided to discontinue the 440/50 mg development and develop two new tablet formulations; one containing 220 mg of naproxen sodium with 25 mg of DPH (the 220/25 formula) to be administered as a two-tablet dose and the second containing 220 mg of naproxen sodium with 50 mg of DPH (the 220/50 formula) administered as a one-tablet dose. Based on the results of the clinical study, the 220/25 formula, administered as a two-tablet dose, was selected as the final product for commercialization.

The bioavailability of the naproxen sodium/DPH combination product was evaluated under fed and fasted conditions in Study 16135.

The naproxen/DPH tablets used in the pivotal clinical studies, however, were over-encapsulated for blinding purposes. The comparative dissolution profile data for the over-encapsulated and un-encapsulated tablets are summarized in the following tables and figures.

Table 1. Data Table for Dissolution Profiles of Un-encapsulated Tablets and Over-encapsulated Tablets – Naproxen Sodium Dissolution

Time (minutes)	Un-encapsulated Tablets (Batch # 59541P0)		Over-encapsulated 59541P0 Tablets (Batch # 130911-003)	
	Average %Released	%RSD	Average %Released	%RSD
10	(b) (4)			
15				
20				
30				
45				
60				

Table 2. Data Table for Dissolution Profiles of Un-encapsulated Tablets and Over-encapsulated Tablets – Diphenhydramine HCl Dissolution

Time (minutes)	Un-encapsulated Tablets (Batch # 59541P0)		Over-encapsulated 59541P0 Tablets (Batch # 130911-003)	
	Average %Released	%RSD	Average %Released	%RSD
10	(b) (4)			
15				
20				
30				
45				
60				

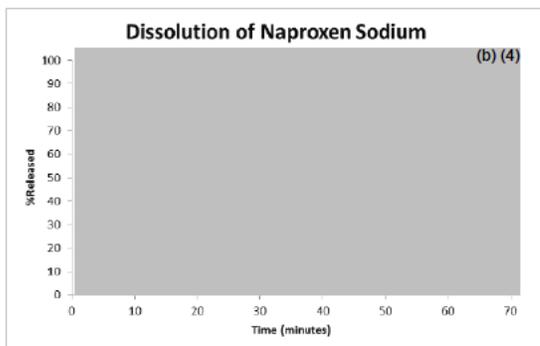


Figure 1. Naproxen Sodium Dissolution Profile

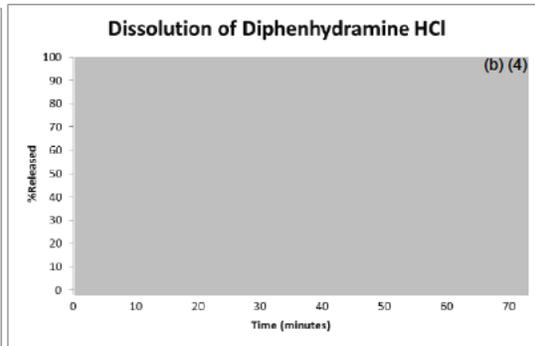


Figure 2. Diphenhydramine HCl Dissolution Profile

The Applicant calculated f_2 metric was $\frac{(b)}{(4)}$ for naproxen sodium dissolution comparison and $\frac{(b)}{(4)}$ for diphenhydramine HCl dissolution comparison.

Reviewer’s Evaluation: Satisfactory. *The clinical tablet formulation is the to-be-marketed tablet formulation. There were no changes to the tablet composition or significant changes to the manufacturing process (minor differences in scale and equipment were noted). These differences were reflected in the registration stability batches, whose dissolution performance was visually similar to that of a representative clinical lot. Relative bioavailability data for the proposed NDA product, as per CFR 320.21, were included in the submission. Further, over-encapsulation did not result in significant differences in drug release, when the data are analyzed using an FDA accepted model independent statistical approach. This Reviewer’s calculated f_2 value was 58 for naproxen and 67 for DPH, which differed from the Applicant because this Reviewer’s calculation did not include data points with >20% variability and was limited to only one data point with > $\frac{(b)}{(4)}$ % dissolution.*

3.0 INFORMATION REQUESTS DURING THE REVIEW

The following review issues were communicated to the Applicant during the review. The Applicant’s response information was incorporated into the body of the review. All responses were satisfactory and there are no outstanding review issues.

31 May 2013 IR (Day 74 Letter) – Responses Included in the 15 July 2013 Amendment (Letter dated 15 July 2013)

1. Your dissolution method development and validation information is incomplete. Please provide the following:
 - The complete dissolution method development report, which includes your data-based justification for the selected dissolution apparatus and agitation speed as optimal for your product, and provide the pH solubility profile of each drug substance. FDA was only able to locate your justification for the proposed dissolution medium in the NDA.
 - The results of the studies completed to evaluate the discriminating ability (i.e., the method’s ability to detect meaningful manufacturing variations) of your proposed dissolution method for review.

2. Your batch analyses and stability data include only single-point dissolution at (b) (4) minutes, which is inadequate for review. Provide the complete dissolution profile data for each pivotal clinical and registration batch (10, 15, 20, 30, 45, and 60 minutes) at release. If release data are not available, we request that you collect the dissolution data using appropriate remaining samples. The source and storage conditions for the samples used should be specified. Also, add complete dissolution profile sampling to your next and future stability pulls and provide an update in a future amendment to your NDA.

3 September 2013 IR - Responses Submitted in the 1 October 2013 Amendment (Letter dated 26 September 2013)

1. We note that over-encapsulated tablets were used in your pivotal clinical studies. However, we are unable to locate any data bridging the capsule formulation with the proposed commercial tablet. Provide the comparative dissolution profile data (individual values, mean, RSD, f2 statistic) using the proposed dissolution method for the over-encapsulated clinical trial material compared with the un-encapsulated referenced tablets (lot 59541P0) (n =12) demonstrating similar dissolution performance between the products. Please note that significant differences in dissolution may need to be further supported with bioequivalence data.
2. Your proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at (b) (4) minutes is not acceptable. Absent clinical data to justify wider tolerances, the dissolution acceptance criterion should reflect the earliest time point where $> \frac{(b)}{(4)}\%$ dissolution is occurring. Your data support a final acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes for both APIs. Implement this change and provide a revised drug product specification table incorporating the updated dissolution acceptance criterion.

SUPPLEMENTAL TABLES AND FIGURES

Table 10: Batches to Support the Clinical Trials for the 220/25 and 220/50 Formulations

Over-encapsulated Product Batch #	Active Material	(b) (4)	Purpose				
56541H0	Aleve PM 220/25 PH100009			<ul style="list-style-type: none"> • Efficacy • MUST • Dose Ranging 			
59541J0	Aleve PM 220/50 PH100010				<ul style="list-style-type: none"> • Efficacy • MUST • Dose Ranging 		
59541G0	Aleve 220mg					<ul style="list-style-type: none"> • Efficacy • MUST • Dose Ranging 	
59541L0	DPH 50mg						<ul style="list-style-type: none"> • Efficacy • MUST • Dose Ranging
59541F0	Not applicable						

Representative sample of the dissolution data used for setting the acceptance criterion:

Dissolution data at 20, 30, and 45 minutes for Clinical batch 59541P0 (Section P.2.2.2 page 9 of 28) - Age not specified

Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
20min-1		(b) (4)
20min-2		
20min-3		
20min-4		
20min-5		
20min-6		
20min-7		
20min-8		
20min-9		
20min-10		
20min-11		
20min-12		
Average		
Min-Max		
Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
30min-1		(b) (4)
30min-2		
30min-3		
30min-4		
30min-5		
30min-6		
30min-7		
30min-8		
30min-9		
30min-10		
30min-11		
30min-12		
Average		
Min-Max		
Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
45min-1		(b) (4)
45min-2		
45min-3		
45min-4		
45min-5		
45min-6		
45min-7		
45min-8		
45min-9		
45min-10		
45min-11		
45min-12		
Average		
Min-Max		

Dissolution data at 20, 30, and 45 minutes for Registration lot 6662 (Development Report Section P.2.2.2 page 45 of 53) - Age not specified

Registration Lot 6662

Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
20min-1		(b) (4)
20min-2		
20min-3		
20min-4		
20min-5		
20min-6		
20min-7		
20min-8		
20min-9		
20min-10		
20min-11		
20min-12		
Average		
% RSD		
Min-Max		
Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
30min-1		(b) (4)
30min-2		
30min-3		
30min-4		
30min-5		
30min-6		
30min-7		
30min-8		
30min-9		
30min-10		
30min-11		
30min-12		
Average		
% RSD		
Min-Max		

Registration Lot 6662 continued.

Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
45min-1	(b) (4)	
45min-2		
45min-3		
45min-4		
45min-5		
45min-6		
45min-7		
45min-8		
45min-9		
45min-10		
45min-11		
45min-12		
Average		
% RSD		
Min-Max		

Dissolution data at 20, 30, and 45 minutes for Registration lot 6664 (Section P.2.2.2 page 26 of 28) - 12 months storage.

Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
20min-1	(b) (4)	
20min-2		
20min-3		
20min-4		
20min-5		
20min-6		
20min-7		
20min-8		
20min-9		
20min-10		
20min-11		
20min-12		
Average		
Min-Max		
Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
30min-1	(b) (4)	
30min-2		
30min-3		
30min-4		
30min-5		
30min-6		
30min-7		
30min-8		
30min-9		

Registration Lot 6664 continued.

30min-10	(b) (4)	
30min-11		
30min-12		
Average		
Min-Max		
Sample No.	Naproxen Sodium %Released	Diphenhydramine HCl %Released
45min-1	(b) (4)	
45min-2		
45min-3		
45min-4		
45min-5		
45min-6		
45min-7		
45min-8		
45min-9		
45min-10		
45min-11		
45min-12		
Average		
Min-Max		

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/s/

MINERVA HUGHES
12/06/2013

ANGELICA DORANTES
12/06/2013

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	205,352	Brand Name	Aleve PM™
OCP Division (I, II, III, etc.)	DCP-I	Generic Name	Naproxen sodium / Diphenhydramine hydrochloride
Medical Division	DNCE	Drug Class	Nonsteroidal anti- inflammatory drugs / H1-receptor antagonist
OCP Reviewer	Xinning Yang	Indication(s)	Relief of occasional sleeplessness when associated with minor aches and pains; Help fall asleep and stay asleep. for adults and children 12 years of age and above as OTC product
OCPB Team Leader	Angela Y. Men	Dosage Form	Naproxen sodium 220 mg/ Diphenhydramine hydrochloride 25 mg tablet (film-coated immediate- release tablet)
		Dosing Regimen	2 tablets before bedtime for no more than 10 consecutive days
Date of Submission	03/20/2013	Route of Administration	Oral
Estimated Due Date of OCP Review	11/7/2013	Sponsor	Bayer Healthcare Consumer Care
Division Due Date	11/20/2013	Priority Classification	Standard
PDUFA Due Date	1/20/2014		

Clin. Pharm. and Biopharm. Information

The applicant, Bayer HealthCare Consumer Care (Bayer), filed this NDA for a nighttime analgesic/sleep-aid, fixed-combination, over-the-counter (OTC) drug product containing naproxen sodium 220 mg and diphenhydramine hydrochloride (DPH) 25 mg per tablet (film-coated, immediate-release tablet). 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 before bedtime for no more than 10 consecutive days.

Naproxen sodium is a member of the non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic, anti-inflammatory, and antipyretic properties. DPH is an H1-receptor antagonist used as a sedative, hypnotic, antihistamine, and antiemetic agent in some OTC products. Currently, there is no combination product available in the US that combines naproxen sodium with DPH.

The clinical development program included a pilot efficacy study (13053), 2 pivotal efficacy studies (14837 and 15881), a multiple-dose safety study (15560), and a pharmacokinetic (PK) study (16135). These clinical studies were conducted to demonstrate the superior efficacy of naproxen sodium 440 mg/DPH 50 mg combination product over its individual ingredients and a safety and tolerability profile similar to that of the individual ingredients. Fixed combination products, naproxen sodium 220 mg /DPH 25 mg and naproxen 220 mg /DPH 50 mg, were used in these studies except Study 13053 where commercial products Aleve[®] (naproxen sodium 220 mg tablet) and Benadryl[®] (DPH 25 mg tablet) were administered concomitantly.

Study 16135 was a Phase 1, randomized, open-label, single-dose, 4-way cross-over study conducted in healthy adult subjects. The objectives were to determine and compare the PK profiles of a single oral dose of naproxen sodium 220 mg/DPH 25 mg (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 440 mg and DPH 50 mg in the combination product.

There is no drug-drug interaction for the combination product versus the single ingredient products. The 90% CIs of the geometric mean ratio for naproxen C_{max} (87.9, 98.3), AUC_{0-inf} (99.8, 105.2), and AUC_{0-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-inf} (97.1, 107.1), and AUC_{0-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%.

Food (high-fat meal) had no effect on the overall exposure of naproxen or DPH in the combination product, however, there is a delay in the rate of absorption with a lower (19%) peak exposure of naproxen and a higher (13%) peak exposure of DPH in the presence of food. The 90% CIs of the geometric mean ratio for AUC_{0-inf} and AUC_{0-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. The 90% CIs of the geometric mean ratio for C_{max} of naproxen were (76.1, 85.1), and for DPH were (102.2, 125.4), when comparing naproxen sodium 440 mg/DPH HCl 50 mg under fed conditions relative to fasted conditions. In the presence of food, the median of T_{max} was delayed from 1.25 (range: 0.33 – 3.0) hrs to 3.0 (0.75 – 6.0) hrs for naproxen. The T_{max} of DPH was less affected, being 2.5 (1.0 – 4.0) hrs under fasted state and 2.5 (1.25 – 6.0) hrs under fed condition.

Filability and QBR comments		
	“X” if yes	Comments
Application filable?	X	
Comments sent to firm?		Information request was sent to the applicant requiring submission of the validation reports for the bioassays used to analyze PK samples from Study 16135, and submission of datasets in xpt format for raw PK data and PK parameters. The applicant submitted the required documents on May 15, 2013.
QBR questions (key issues to be considered)		
Other comments or information not included above		No driving test or next-day residual effect study was conducted. The sponsor reviewed available published data on DPH’s potential effects on psychomotor performance and driving when used as a sleep-aid, and provided a summary report.
Primary reviewer Signature and Date	Xinning Yang	
Secondary reviewer Signature and Date	Angela Y. Men	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Xinning Yang	05/09/2013
Reviewing Clinical Pharmacologist	Date

Angela Y. Men	05/09/2013
Team Leader/Supervisor	Date

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/s/

XINNING YANG
05/22/2013

YUXIN MEN
05/29/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	NDA 205-352
Submission Date	20 March 2013
Product name, generic name of the active	Naproxen Sodium/diphenhydramine (proposed name Aleve PM)
Dosage form and strength	Tablet – Immediate Release (220/25 mg)
Applicant	Bayer HealthCare
Clinical Division	Division of Nonprescription Clinical Evaluation
Type of Submission	NDA 505(b)2
Primary Biopharmaceutics Reviewer	Minerva Hughes, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Assignment Date	15 April 2013
Filing Date	19 May 2013
Filing Review Date	10 May 2013
Filing Recommendation	Fileable

I. SUBMISSION OVERVIEW

NDA 205-352 was submitted in accordance with Section 505(b)2 of the FDC Act for the use of naproxen sodium and diphenhydramine (DPH) as a fixed dose combination to relieve occasional sleeplessness associated with minor aches and pains. Naproxen sodium has been marketed as an over-the counter (OTC) product in the US since 1994 and is currently approved for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, and backache; for the minor pain of arthritis; for the pain of menstrual cramps; and for the reduction of fever. Naproxen sodium is approved in the US at OTC doses of 220 mg and 440 mg for use by adults and children at least 12 years of age or older. DPH, under the brand name Benadryl, received marketing approval in the US in 1946 for use as a prescription antihistamine and was later monographed in 1982 for use as a sleep aid at a dose of 50 mg (21 CFR 338).

There are several OTC analgesic + nighttime sleep-aid combination products available in the US indicated for pain accompanied by sleeplessness. Examples include Advil PM (ibuprofen 200 mg + diphenhydramine citrate 38 mg), Tylenol PM (acetaminophen 500 mg + diphenhydramine HCl 25 mg), Bayer PM (aspirin 500 mg + diphenhydramine citrate 38 mg), Motrin PM (ibuprofen 200 mg + diphenhydramine citrate 38 mg), and Excedrin PM (acetaminophen 500 mg + diphenhydramine citrate 38 mg). Currently, there are no OTC analgesic + nighttime sleep-aid combination products available in the US that combine naproxen sodium with DPH.

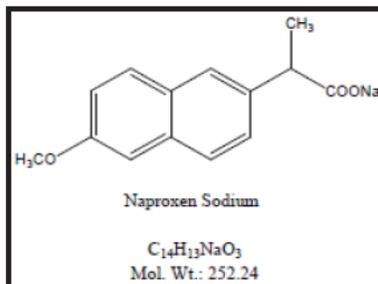
II. BIOPHARMACEUTICS SUMMARY INFORMATION

Reference was made to DMF (b) (4) for naproxen sodium drug substance CMC information and to DMF (b) (4) for diphenhydramine hydrochloride.

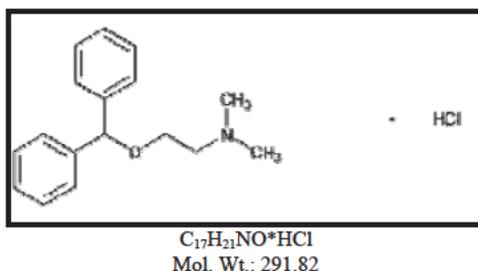
Naproxen sodium is a member of the arylpropionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs) with analgesic, anti-inflammatory, and antipyretic properties. The drug substance has good aqueous solubility (pH dependent) and, as a single agent, is rapidly absorbed following oral administration with an in vivo bioavailability of 95%.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

The chemical structure and formula is illustrated below.



DPH is an H₁-receptor antagonist of the ethanolamine class used as a sedative, hypnotic, antihistamine, antitussive, and antiemetic agent in OTC products. It is also well absorbed following oral administration, 72% in vivo bioavailability, and is very soluble in water. The chemical structure and formula is illustrated below.



The proposed drug product is a blue, film-coated tablet comprised of the active ingredients naproxen sodium (220 mg) and DPH (25 mg) and the excipients microcrystalline cellulose, povidone, talc, magnesium stearate, carnauba wax, and (b) (4). The intended therapeutic dose is two tablets just before bed. Tablets are manufactured by (b) (4).

Finished tablets are packaged in HDPE bottles. The drug product release specification includes tests for appearance, identification, assay, uniformity of dosage units, dissolution, impurities, and microbial purity.

During development, (b) (4)

(b) (4) The to-be-marketed formulation/process was used in the pivotal clinical studies.

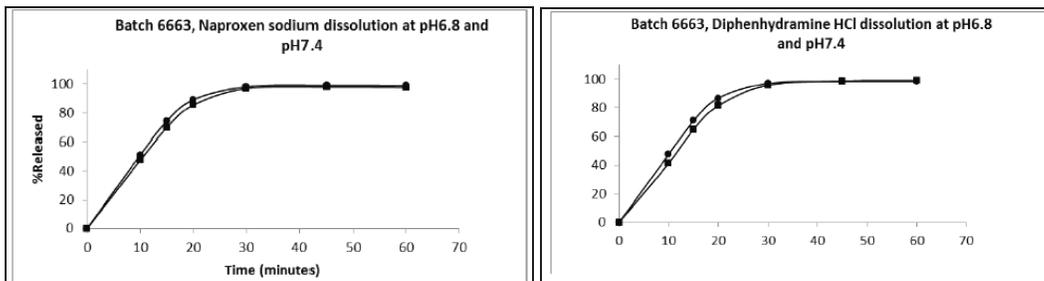
This Biopharmaceutics review will evaluate the adequacy of the proposed dissolution method and acceptance criteria to assure product quality.

The proposed dissolution method and acceptance criterion are as follows.

- USP Apparatus II, 100 mM Sodium Phosphate Buffer, pH 7.4, 900 mL, 75 rpm
- Q = (b) (4)% at (b) (4) minutes = naproxen sodium
- Q = (b) (4)% at (b) (4) minutes = DPH

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

A representative dissolution profile is illustrated below.



III. POTENTIAL REVIEW ISSUES – DAY 74 LETTER COMMENTS

The Applicant's dissolution method development and validation information is incomplete. The following comments should be included in the Day 74 letter for the Applicant to address.

- (1) *Provide the complete dissolution method development report, which includes your data-based justification for the selected dissolution apparatus and agitation speed as optimal for your product, and provide the pH solubility profile of each drug substance. FDA was only able to locate your justification for the proposed dissolution medium in the NDA.*
- (2) *Provide the results of the studies completed to evaluate the discriminating ability (i.e., the method's ability to detect meaningful manufacturing variations) of your proposed dissolution method for review.*
- (3) *Your batch analyses and stability data include only single-point dissolution at 60 minutes, which is inadequate for review. Provide the complete dissolution profile data for each pivotal clinical and registration batch (10, 15, 20, 30, 45, and 60 minutes) at release. If release data are not available, we request that you collect the dissolution data using appropriate remaining samples. The source and storage conditions for the samples used should be specified. Also, add complete dissolution profile sampling to your next and future stability pulls and provide an update in a future amendment to your NDA.*

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

IV. FILING REVIEW CHECKLIST

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	YES	NO	COMMENT
1.	Does the application contain dissolution data?	X		
2.	Is the dissolution test part of the DP specifications?	X		USP Apparatus II, 100 mM Sodium Phosphate Buffer, pH 7.4, 900 mL, 75 rpm Q = (b)(4)% at (b)(4) minutes = naproxen sodium Q = (b)(4)% at (b)(4) minutes = DPH
3.	Does the application contain the dissolution method development report?	X		The dissolution method only discusses optimizing the medium pH. There is no information on apparatus, agitation selection. Nor were studies on the method's discriminating ability located.
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?		X	
6.	Does the application include a IVIVC model?		X	
7.	Is information such as BCS classification mentioned, and supportive data provided?		X	
8.	Is information on mixing the product with foods or liquids included?		X	
9.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		Study 16135 – fed/fasted BA study using the fixed dose combination (<i>will be reviewed by the Clinical Pharmacology Reviewer</i>)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	YES	NO	COMMENT
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping? c.) Is there a site comparability protocol?		X	

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
11.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
13.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		See above list (page 3).

{See appended electronic signature page}

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

MINERVA HUGHES
05/10/2013

ANGELICA DORANTES
05/10/2013