

Pharmacokinetics of naproxen and esomeprazole in PN400, a single-tablet, multilayer formulation of enteric-coated naproxen coupled with immediate-release esomeprazole

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Abstract

Introduction: PN400 is a single-tablet formulation with an enteric-coated (EC) naproxen core surrounded by an immediate-release (IR) esomeprazole mantle designed for initial and rapid release of esomeprazole in the stomach followed by release of EC naproxen after esomeprazole absorption. The aim of this study was to determine levels of exposure of esomeprazole and naproxen when used in combination in PN400 and with EC esomeprazole + naproxen 500 mg.

Methods: This randomized, open-label, 9-day, four-way crossover, single-center study enrolled 28 healthy *H. pylori*-negative adults without a history of peptic ulcer/acid-related gastrointestinal symptoms. Subjects were randomized to different sequences of the following: A) PN400/E30 [EC naproxen 500 mg/IR esomeprazole 30 mg] BID; B) PN400/E20 [EC naproxen 500 mg/IR esomeprazole 20 mg] BID; C) PN400/E10 [EC naproxen 500 mg/IR esomeprazole 10 mg] BID; and D) EC E20 [EC esomeprazole 20 mg] QD + non-EC naproxen 500 mg BID. Blood samples were taken on Days 1 and 9 before dosing and at various times up to 24 hours afterwards for pharmacokinetic assessments of esomeprazole and naproxen.

Results: Esomeprazole was rapidly absorbed from all three doses of PN400 with measurable plasma concentrations as early as 10 minutes after the AM dose and at 20-30 minutes after the PM dose. Differences in C_{max} and AUCs for esomeprazole from PN400 were generally dose-dependent. As expected, the T_{max} for EC naproxen was delayed in relation to the T_{max} for esomeprazole. Steady-state AUCs for naproxen monocomponent were comparable to all PN400 formulations. T_{max} with non-EC naproxen occurred considerably earlier than with the EC naproxen component of the PN400 formulations. Esomeprazole and naproxen pharmacokinetic parameters for the AM dose on Day 1 and Day 9 are provided in the Table.

	Esomeprazole			Naproxen		
	C_{max} [†] ng/mL	T_{max} [†] hr	AUC _{0-10 AM} [†] hr*ng/mL	C_{max} [†] mcg/mL	T_{max} [†] hr	AUC _{0-10 AM} [†] hr*mcg/mL
PN400/E30	1584 (39)	0.50 (0.17-1.50)	2779 (45)	80.9 (23)	3.00 (0.00-8.00)	603 (21)
PN400/E20	715 (52)	0.50 (0.17-1.50)	1216 (69)	86.2 (22)	3.00 (0.00-8.05)	607 (19)
PN400/E10	278 (57)	0.33 (0.17-1.00)	368 (89)	87.1 (21)	2.50 (0.00-8.00)	637 (17)
EC E20 + naproxen	435 (48)	1.50 (1.00-14.00)	1046 (54)	90.0 (19)	1.50 (0.50-4.00)	617 (12)

†Values are mean (% coefficient of variation) for C_{max} and AUC, and median (range) for T_{max} .

Conclusion: PN400 produced dose-dependent increases in plasma esomeprazole concentrations and similar naproxen concentrations to dosing with EC E20 + naproxen. The pharmacokinetics of esomeprazole administered as the PN400 formulation were consistent with immediate release, and T_{max} for esomeprazole preceded that for EC naproxen.

1. Introduction

- The use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a substantial risk of upper gastrointestinal (GI) adverse events ranging from endoscopic erosions and ulcers to serious ulcer complications such as perforation, obstruction, and bleeding.¹
- The efficacy of proton pump inhibitors (PPIs) (eg, esomeprazole) for the prevention of NSAID-associated endoscopic injury and upper GI symptoms is well-documented.^{2,3}
- Enteric-coated (EC) esomeprazole 20 mg QD has demonstrated clinical efficacy in the prevention of gastroduodenal ulcers in at-risk patients using NSAIDs.⁴
- PN400 is a single-tablet, fixed-dose formulation of an EC naproxen 500 mg core surrounded by an immediate-release (IR) esomeprazole mantle, designed to provide sequential delivery of gastroprotective esomeprazole before exposure to naproxen.
- This study evaluated the pharmacodynamics, pharmacokinetics, and safety of three different dose formulations of PN400. Here we present the pharmacokinetic and safety findings of the study (the pharmacodynamic data are presented in poster T1969).
- The aim of this study was to determine levels of exposure of esomeprazole and naproxen, and time to exposure to these drugs, when used in combination in PN400 and with naproxen 500 mg + EC esomeprazole (20 mg).

2. Methods

Study design

- This was a prospective, randomized, Phase I, open-label, single-center, cross-over study comprising four treatment periods.
- On Day 1 of the first treatment period, patients were randomized into one of four treatment sequences to receive each of the following treatments for 9 days in a cross-over fashion, with a washout period of ≥14 days between treatments:
 - PN400/E30 (EC naproxen 500 mg/IR esomeprazole 30 mg) BID
 - PN400/E20 (EC naproxen 500 mg/IR esomeprazole 20 mg) BID
 - PN400/E10 (EC naproxen 500 mg/IR esomeprazole 10 mg) BID
 - Naproxen + EC E20 (non-EC naproxen 500 mg BID and EC esomeprazole 20 mg QD).
- Study medication was administered 60 minutes before meals in the morning and evening.

Patients

- Eligible patients were healthy adults aged 18-55 years who tested negative for *Helicobacter pylori* infection and had no history of peptic ulcer disease or other GI symptoms.
- Patients with a history of hypersensitivity, allergy, or intolerance to any NSAID or PPI were excluded from this study.

End points

- Pharmacokinetic parameters (C_{max} , T_{max} , and AUC_{0-10 AM}/AUC_{0-14 PM}) for esomeprazole and naproxen following the three PN400 treatments, and the naproxen + EC E20 treatment on Day 1 and Day 9.
- Safety of each treatment group was assessed using clinical adverse events, as well as physical examination, vital signs, and clinical laboratory tests.
- Other end points included pharmacodynamics (primary end point was percent of time on Day 9 in which intra-gastric pH was >4.0; secondary end point was the percent of time on Day 1 in which intra-gastric pH was >4.0) and safety. (Pharmacodynamics are presented in Poster T1969).

Statistical analysis

- The primary analysis was performed using Analysis of Variance (ANOVA) to determine the point estimate and 90% CI of the Day 9 to Day 1 ratios for both esomeprazole and naproxen.
- Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 8.0) for system organ class and preferred term.
- The safety analysis was based on the safety population.

3. Results

Patient disposition

- Twenty-eight subjects were randomized to treatment and were included in the safety, pharmacokinetics, and intent-to-treat (ITT) populations.
- The study was completed by 27 subjects and 25 subjects were included in the per-protocol (PP) population; the three patients excluded from the PP population were
 - one who withdrew because of personal reasons
 - one who became ill during the study
 - one with invalid intra-gastric pH data.

Patient demographics

- Baseline characteristics of enrolled subjects are outlined in Table 1.

	Total Subjects N=28
Age (years)	24.9 (3.9)
Mean (SD)	24
Median	18-34
Range	
Gender, n (%)	
Males	19 (68)
Females	9 (32)
Race, n (%)	
White	28 (100)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	0
Not Hispanic or Latino	28 (100)
Height (in)	
Mean (SD)	70.1 (4.1)
Median	70
Range	63-79
Weight (lb)	
Mean (SD)	177.9 (34.6)
Median	178
Range	112-250

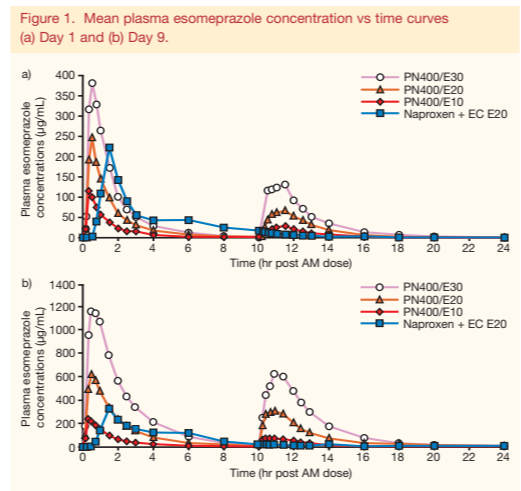
SD, standard deviation.

Esomeprazole

Pharmacokinetic evaluations

- Day 1:
 - measurable plasma concentrations of esomeprazole were obtained rapidly with all three PN400 treatments—at 10 minutes after the AM dose and at 20-30 minutes after administration of the PM dose.
 - esomeprazole was rapidly eliminated from plasma in the majority of subjects by 6-8 hours post-dose (AM and PM) for all three PN400 treatments (Figure 1a).
- Day 9:
 - pre-AM dose samples showed that esomeprazole concentrations were measurable in 19 subjects receiving PN400/E30 treatment, 13 receiving PN400/E20 treatment, and 6 receiving PN400/E10 treatment.
 - post- AM and PM dose samples showed that, in the PN400 treatments containing higher esomeprazole doses (PN400/E30 and PN400/E20), plasma concentrations of esomeprazole were measurable at earlier post-dose time points in a large number of subjects and for a longer period compared with Day 1.

- Following AM or PM doses on Day 1 and Day 9, plasma esomeprazole concentrations increased with the esomeprazole dose for all three PN400 treatments. On both days, the measurable plasma concentrations of esomeprazole were higher following the AM dose than the PM dose for all three PN400 treatments (Figure 1a and 1b).
- Following naproxen + EC E20 treatment on Day 1 and Day 9, measurable plasma concentrations of esomeprazole were not available until 0.75-1.5 hours post-dose in the majority of subjects and were measurable for longer than concentrations following PN400 administration (Figure 1a and 1b). The plasma esomeprazole profile exhibited was consistent with that of a delayed-release formulation.



Pharmacokinetic parameters

- The pharmacokinetic parameters of esomeprazole for all PN400 treatments following administration of the AM and PM doses on Day 1 and Day 9 are summarized in Table 2.

Table 2. Summary of esomeprazole pharmacokinetic parameters. Values are Mean (% coefficient of variation) for C_{max} and AUC, and Median (range) for T_{max} .

Treatment type	Day, Dose	C_{max} (ng/mL)	T_{max} (hr)	AUC _{0-10 AM} or AUC _{0-14 PM} (hr*ng/mL)
PN400/E30 n=28	Day 1, AM	487 (82)	0.50 (0.33-1.50)	591 (108)
	Day 1, PM	187 (132)	1.50 (0.33-4.00)	388 (137)
PN400/E20 n=28	Day 1, AM	292 (77)	0.50 (0.20-1.50)	350 (113)
	Day 1, PM	96.6 (104)	1.49 (0.33-3.00)	206 (141)
PN400/E10 n=27	Day 1, AM	138 (71)	0.33 (0.17-3.10)	148 (111)
	Day 1, PM	35.3 (84)	1.50 (0.33-3.00)	85.7 (179)
Naproxen + EC E20 n=28	Day 1, AM	282 (66)	1.50 (1.00-16.00)	520 [†] (64)
	Day 9, AM	1584 (39)	0.50 (0.17-1.50)	2779 (45)
PN400/E30 n=28	Day 9, PM	810 (59)	1.00 (0.33-8.00)	2066 (53)
	Day 9, AM	715 (52)	0.50 (0.17-1.50)	1216 (69)
PN400/E20 n=27	Day 9, PM	428 (73)	0.75 (0.33-3.00)	919 (84)
	Day 9, AM	278 (57)	0.33 (0.17-1.00)	368 (89)
PN400/E10 n=27	Day 9, PM	97.6 (136)	1.00 (0.33-2.00)	223 [†] (134)
	Day 9, AM	435 (48)	1.50 (1.00-14.00)	1046 (54)

[†]n=26; n=27.

- C_{max} for esomeprazole plasma concentration occurred approximately 0.5 hours post-AM dose, and between 1.0-1.5 hours post-PM dose on Day 1 and Day 9 for all three PN400 treatments.
- Esomeprazole C_{max} and AUCs were higher following the AM dose than the PM dose on Day 1 and Day 9 for all three PN400 treatments and were dose-dependent.

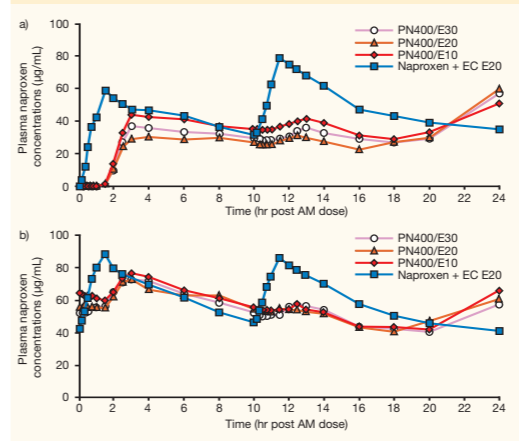
- Esomeprazole concentrations were higher on Day 9 than Day 1 for each PN400 treatment.
- Following treatment with naproxen + EC E20, C_{max} for esomeprazole plasma concentrations were observed at approximately 1.5 hours post-dose (1 hour later than the PN400 treatments).

Naproxen

Pharmacokinetic evaluations

- Day 1, AM dose:
 - measurable plasma concentrations of naproxen were first detected at approximately 2 hours post-PN400 administration for all three PN400 treatments (Figure 2a).
- Day 9:
 - pre-AM dose samples showed that naproxen concentrations were measurable in all subjects and were measurable throughout the entire sampling time.
- The mean plasma profiles of naproxen were comparable following the three PN400 treatments, particularly on Day 9 (Figure 2a and 2b), demonstrating delayed-release characteristics consistent with the formulation design of PN400. The higher mean naproxen plasma concentrations observed at the end of a 24-hour daily interval resulted from the delayed absorption of naproxen from PN400 (Figure 2a and 2b).

Figure 2. Mean plasma naproxen concentration vs time curves (a) Day 1 and (b) Day 9.



- Mean plasma concentrations of naproxen were much higher on Day 9 than on Day 1 (Figure 2a and 2b).
- Following naproxen + EC E20 treatment on Day 1, plasma naproxen concentrations were measurable in all subjects at the 10-minute post-dose sample time and for up to 24 hours, consistent with a non-EC naproxen formulation.
- Following AM and PM doses on Day 1 and Day 9, mean plasma naproxen concentrations were higher and occurred earlier following naproxen + EC E20 treatment than with any of the PN400 treatments (Figure 2a and 2b).

Pharmacokinetic parameters

- The pharmacokinetic parameters of naproxen for all PN400 treatments following administration of the AM and PM doses on Day 1 and Day 9 are summarized in Table 3.
- C_{max} for naproxen plasma concentration occurred approximately 3-4 hours post-AM dose, and between 10-14 hours post-PM dose on Day 1 and Day 9 for all three PN400 treatments. The delay in naproxen absorption was consistent with the EC naproxen in the PN400 formulations.
- Naproxen C_{max} and AUCs post- AM and PM doses on Day 1 and Day 9 were comparable among all three PN400 treatments, consistent with the same dose of naproxen in each formulation.
- Following treatment with EC E20 + naproxen, naproxen was quickly absorbed, with peak plasma concentrations observed at 1.5 hours post-dose on Day 1 and Day 9.

Safety

- Adverse events are summarized in Table 4.
- No serious adverse events were reported and no patients withdrew from the study due to adverse events.
- Most laboratory abnormalities were small deviations from the normal range.
- Vital sign measurements and physical examination findings were similar at screening and the final visit.

Table 3. Summary of naproxen pharmacokinetic parameters. Values are Mean (% coefficient of variation) for C_{max} and AUC, and Median (range) for T_{max} .

Treatment type	Day, Dose	C_{max} (ng/mL)	T_{max} (hr)	AUC _{0-10 AM} or AUC _{0-14 PM} (hr*ng/mL)
PN400/E30 n=28	Day 1, AM	48.1 (53)	4.00 (2.00-10.00)	259 (56)
	Day 1, PM	68.9 (28)	14.00 (0.50-14.00)	471 (30)
PN400/E20 n=28	Day 1, AM	44.4 (68)	4.00 (2.00-10.00)	231 (70)
	Day 1, PM	71.5 (26)	14.00 (0.00-14.00)	450 (33)
PN400/E10 n=27	Day 1, AM	57.0 (31)	4.00 (2.00-10.00)	310 (35)
	Day 1, PM	68.6 (26)	10.00 (0.00-14.00)	508 (29)
Naproxen + EC E20 n=28	Day 1, AM	65.5 (25)	1.50 (0.75-6.00)	409 (16)
	Day 1, PM	81.5 (14)	1.50 (0.50-2.50)	685 (10)
PN400/E30 n=28	Day 9, AM	80.9 (23)	3.00 (0.00-8.00)	603 (21)
	Day 9, PM	76.2 (23)	10.40 (0.00-14.00)	648 (20)
PN400/E20 n=27	Day 9, AM	86.2 (22)	3.00 (0.00-8.05)	607 (19)
	Day 9, PM	76.8 (18)	10.00 (0.00-14.00)	678 (16)
PN400/E10 n=27	Day 9, AM	87.1 (21)	2.50 (0.00-8.00)	637 (17)
	Day 9, PM	78.6 (17)	14.00 (1.50-14.00)	672 (19)
Naproxen + EC E20 n=28	Day 9, AM	90.0 (19)	1.50 (0.5-4.00)	617 (12)
	Day 9, PM	86.5 (13)	1.50 (0.75-4.00)	769 (10)

Table 4. Clinical adverse events reported by >1 subject (greater than 4%) on any treatment

Adverse event, n (%)	PN400/E30 (n=28)	PN400/E20 (n=28)	PN400/E10 (n=27)	Naproxen + EC E20 (n=28)
≥1 adverse event	14 (50)	14 (50)	9 (33)	8 (29)
Gastrointestinal disorders	9 (32)	8 (29)	8 (30)	5 (18)
Diarrhea	4 (14)	4 (14)	3 (11)	2 (7)
Abdominal distension	2 (7)	2 (7)	2 (7)	2 (7)
Dyspepsia	1 (4)	2 (7)	1 (4)	1 (4)
Abdominal pain (upper)	3 (11)	0	1 (4)	0
Gastroenteritis (viral)	0	0	2 (7)	0
Metabolism and nutrition disorders	3 (11)	5 (18)	1 (4)	1 (4)
Iron deficiency	3 (11)	5 (18)	1 (4)	1 (4)
Nervous system disorders	4 (14)	1 (4)	0	0
Headache	3 (11)	1 (4)	0	0

4. Conclusions

- Esomeprazole was rapidly absorbed following administration of the three PN400 treatments—plasma concentrations were measurable as early as 10 minutes after dose, consistent with an immediate-release formulation; elimination of esomeprazole from plasma occurred between 6-8 hours post dose.
- Esomeprazole C_{max} and AUC following administration of PN400 were dose-dependent; esomeprazole concentrations were higher on Day 9 than on Day 1 for each of the PN400 treatments.
- The naproxen plasma concentration vs time profiles were comparable across all three PN400 treatments; higher concentrations were observed at the end of a 24-hour daily interval, consistent with delayed-release characteristics.
- Esomeprazole T_{max} for all three PN400 treatments occurred approximately 1 hour earlier than that observed for naproxen + EC E20.
- PN400 was well tolerated with no serious adverse events.
- These findings support the ongoing evaluation of PN400 in patients at risk for developing NSAID-associated ulcers.

References

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