

# Gastric acid suppression with PN400, a single-tablet, multilayer, fixed-dose formulation combining an immediate-release esomeprazole layer and an enteric-coated naproxen core

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## Abstract

**Introduction:** Enteric-coated (EC) esomeprazole 20 mg QD has proven clinical efficacy to reduce occurrence of NSAID-associated gastric ulcers. PN400 is a single-tablet, fixed-dose formulation consisting of an immediate-release (IR) esomeprazole mantle surrounding a 500-mg EC naproxen core designed to provide sequential delivery of esomeprazole and naproxen. The aim of this study was to determine the lowest pharmacodynamically effective dose of esomeprazole in PN400 to provide gastric acid suppression similar to a known clinically effective dose of EC esomeprazole (20 mg).

**Methods:** This prospective, 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 the following (with ≥14-day washout period between regimens): 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. The primary end point was the percent of time on Day 9 in which intra-gastric pH was >4.0 (from 24-hour intra-gastric acid measurements).

**Results:** At Day 9, the percentage of time that intra-gastric pH was >4.0 was greater with PN400/E30 BID and PN400/E20 BID than with EC esomeprazole 20 mg QD + naproxen 500 mg BID (95% CIs were positive and did not overlap). PN400/E10 BID was associated with the shortest time during which gastric pH was >4.0, significantly less than that with EC esomeprazole 20 mg QD + naproxen 500 mg BID (95% CIs were negative). Furthermore, PN400/E10 BID was associated with the greatest inter-patient variability. PN400 was generally well tolerated and no unexpected adverse events occurred.

**Conclusion:** PN400/E20 BID was the lowest PN400 esomeprazole dosage to achieve a level of acid suppression comparable to EC esomeprazole 20 mg with appropriate consistency of effect. Surprisingly, unprotected esomeprazole given twice daily provided effective gastric acid suppression at steady state.

Day 9	PN400/E30 (n=25)	PN400/E20 (n=25)	PN400/E10 (n=25)	Naproxen + EC E20 (n=25)
% time pH >4.0				
Mean (SD)	76.50 (12.26)	71.35 (13.01)	40.85 (22.51)	56.85 (10.06)
Median	78.79	70.42	35.76	55.14
Coefficient of variation	16	18	55	18
LS mean (SD)	76.75 (3.02)	71.46 (3.02)	41.09 (3.02)	57.23 (3.02)
Comparison with EC E20 + naproxen				
LS mean difference (SE)	19.52 (3.25)	14.23 (3.25)	-16.14 (3.25)	-
95% CI	13.04, 26.01	7.75, 20.71	-22.26, -9.66	-

## 1. Introduction

▶ Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in the world.<sup>1</sup> However, their use 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.<sup>2,3</sup>

▶ Proton pump inhibitors have well-documented efficacy for the prevention of NSAID-associated endoscopic injury and upper GI symptoms,<sup>4,5</sup> and are recognized as an effective gastroprotective strategy for at-risk patients.<sup>6</sup>

▶ Enteric-coated (EC) esomeprazole 20 mg QD has demonstrated clinical efficacy in the prevention of gastroduodenal ulcers in at-risk patients using NSAIDs.<sup>7</sup> Naproxen is a non-selective NSAID with a well-established efficacy and safety profile.

▶ PN400 is a fixed-dose combination of an EC naproxen 500-mg core with an immediate-release (IR) esomeprazole mantle in a single-tablet formulation that is designed to provide sequential delivery of esomeprazole before exposure to naproxen.

▶ This study evaluated the pharmacodynamics, pharmacokinetics, and safety of three different dose formulations of PN400 with the aim of determining the optimal dose of esomeprazole in PN400 to provide gastric acid suppression similar to EC esomeprazole (20 mg).

## 2. Methods

### Study design

▶ This was a prospective, randomized, Phase I, open-label, single-center, cross-over study comprised of 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

▶ The primary end point was percent of time on Day 9 in which intra-gastric pH was >4.0, as measured over 24 hours by a pH probe placed prior to administration of study medication.

▶ Secondary end points were the percent of time on Day 1 in which intra-gastric pH was >4.0, pharmacokinetics of esomeprazole and naproxen, and safety. (Pharmacokinetics and safety are presented in Poster T1972).

### Statistical analysis

▶ The primary analysis was done on the per-protocol population (PP). End points were summarized by treatment group and analyzed by Analysis of Variance (ANOVA). Least Square (LS) means for each treatment, the difference of LS means between treatment groups, and 95% confidence intervals (CI) were calculated.

## 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 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.

Table 1. Patient demographics (ITT population, N=28)

Age (years)	
Mean (SD)	24.9 (3.9)
Median	24
Range	18-34
Gender, n (%)	
Male	19 (68)
Female	9 (32)
Race, n (%)	
White	28 (100)
Other	0 (0)
Ethnicity, n (%)	
Hispanic or Latino	0 (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.

### Intra-gastric pH on Day 9

▶ Treatment with PN400/E30 and PN400/E20 resulted in a greater length of time with intra-gastric pH >4.0 over 24 hours on Day 9 compared with naproxen + EC E20. Treatment with PN400/E10 resulted in the shortest length of time with pH >4.0, significantly less than with naproxen + EC E20 (Table 2).

Table 2. Percent of time with gastric pH >4.0 over 24 hours on Day 9 (PP population)

% Time pH >4.0	PN400/E30 (n=25)	PN400/E20 (n=25)	PN400/E10 (n=25)	Naproxen + EC E20 (n=25)
Mean (SD)	76.50 (12.26)	71.35 (13.01)	40.85 (22.51)	56.85 (10.06)
Median	78.79	70.42	35.76	55.14
CV	16	18	55	18
Range	49.79-95.32	51.76-97.61	10.30-85.26	40.63-75.51
LS Mean (SE)	76.75 (3.02)	71.46 (3.02)	41.09 (3.02)	57.23 (3.02)
LS Mean difference vs naproxen + EC E20 (SE)	19.52 (3.25)	14.23 (3.25)	-16.14 (3.25)	-
95% CI	13.04-26.01	7.75-20.71	-22.26- (-)9.66	-

PP, per-protocol; SD, standard deviation; LS, least square; SE, standard error; CV, coefficient of variation; CI, confidence interval.

▶ A similar pattern was observed for the percent of time intra-gastric pH was >3.0 and >5.0 on Day 9.

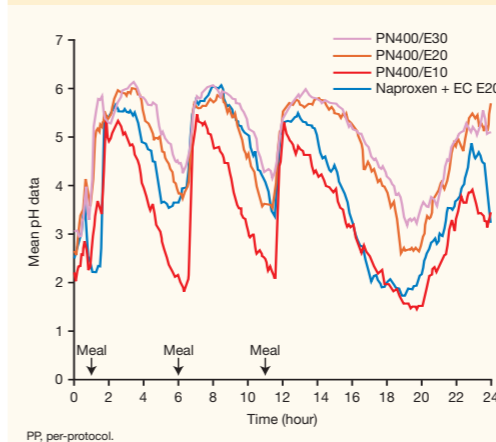
▶ Esomeprazole had a dose-related effect on gastric pH beyond the influence of food intake. Following administration of the morning dose of PN400 formulations, rapid, dose-related increases in pH were observed approximately 1 hour earlier than food-induced increases in pH. In contrast, there was a delay in pH increase following morning administration of naproxen + EC E20 (Figure 1).

▶ PN400/E30 and PN400/E20 had a similar effect on gastric pH with a slower return to low pH levels after food intake compared with PN400/E10 and naproxen + EC E20 (Figure 1).

### Intra-gastric pH on Day 1

▶ In contrast to Day 9, initial doses of esomeprazole had a minimal effect on gastric pH beyond the effect of food intake on Day 1. However, treatment differences began to emerge after the second dose (Figure 2).

Figure 1. Mean intra-gastric pH over 24 hours on Day 9 (PP population)



PP, per-protocol.

▶ Treatment with PN400/E30 resulted in a greater length of time with pH >4.0 over 24 hours on Day 1, compared with naproxen + EC E20. The shortest time with pH >4.0 resulted from treatment with PN400/E10 (Table 3).

▶ A similar pattern was observed for the percent of time intra-gastric pH was >3.0 and >5.0 on Day 1.

Table 3. Percent of time with gastric pH >4.0 over 24 hours on Day 1 (PP population)

% Time pH >4.0	PN400/E30 (n=25)	PN400/E20 (n=25)	PN400/E10 (n=24)	Naproxen + EC E20 (n=25)
Mean (SD)	27.79 (22.63)	20.50 (16.61)	12.81 (11.11)	21.34 (13.63)
Median	19.96	15.26	9.09	16.82
CV	81	81	87	64
Range	1.77-89.61	4.35-74.40	3.00-53.75	3.16-58.20
LS Mean (SE)	27.90 (3.31)	20.58 (3.31)	12.66 (3.35)	21.51 (3.31)
LS Mean difference vs naproxen + EC E20 (SE)	6.39 (3.18)	-0.92 (3.18)	-8.85 (3.22)	-
95% CI	0.04-12.75	-7.28- (-)5.43	-15.28- (-)2.42	-

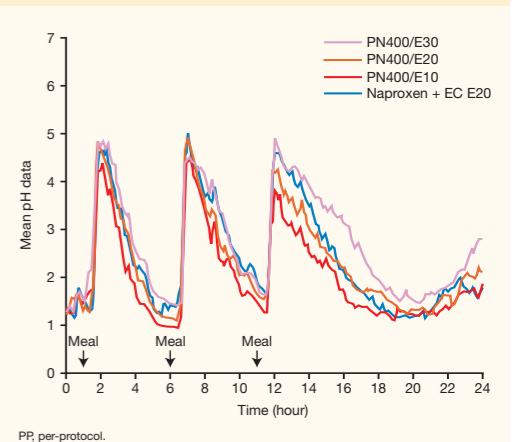
PP, per-protocol; SD, standard deviation; LS, least square; SE, standard error; CV, coefficient of variation; CI, confidence interval.

Table 4. AEs reported by >4% of patients on any treatment (safety population)

AE, n (%)	PN400/E30 (n=28)	PN400/E20 (n=28)	PN400/E10 (n=27)	Naproxen + EC E20 (n=28)
Patients with ≥1 AE	14 (50)	14 (50)	9 (33)	8 (29)
GI disorders	9 (32)	8 (29)	8 (30)	5 (18)
Diarhea	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

AE, adverse event.

Figure 2. Mean intra-gastric pH over 24 hours on Day 1 (PP population)



PP, per-protocol.

### Safety

▶ Adverse events are summarized in Table 4. Safety findings are further described in Poster T1972.

## 4. Conclusions

▶ PN400/E20 BID was the lowest PN400 esomeprazole dosage to achieve a potentially clinically significant level of acid suppression comparable to EC esomeprazole 20 mg with appropriate consistency of effect.

▶ The pharmacodynamic and pharmacokinetic profiles of esomeprazole and naproxen demonstrated that non-EC esomeprazole could be effectively combined with EC naproxen, producing an early onset of increased gastric pH before naproxen is released.

▶ Based on these results, PN400/E20 was selected for further Phase III studies to demonstrate a clinically meaningful reduction in gastroduodenal ulcers in at-risk patients requiring long-term NSAID therapy.

### References

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