

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-507

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

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-507
Brand Name:	Naprapac (Pending)
Generic Name:	Enteric coated (EC) Lansoprazole capsule and Naproxen immediately release (IR) tablets
Dosage form and Strength:	Lansoprazole EC 15 mg capsule plus Naproxen IR 250, 375, or 500 mg tablets
Route of administration:	Oral
Indication:	For treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, in patients with a history of a documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID, such as Naprosyn.
Sponsor:	TAP Pharmaceuticals
Type of submission:	Original
Clinical Division:	GI and Coagulation (HFD-180)
OCPB Division:	HFD-870/DPE II
Priority:	Standard
Submission date:	09/06/02
OCPB Consult date:	09/18/02
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

Lansoprazole is a proton pump inhibitor (PPI). TAP's Prevacid (lansoprazole) enteric coated (EC) 15 and 30 mg capsules are currently on the market indicated for **1)** short-term treatment of gastric or duodenal ulcers, **2)** healing of non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcer, and **3)** for symptomatic gastroesophageal reflux disease (GERD). A dose of 15 or 30 mg is to be given QD before meals.

Naproxen is an NSAID. Roche's Naprosyn (naproxen) immediately release (IR) 250, 375, and 500 mg tablets are also currently on the market as prescription drug indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis and also for the treatment of tendonitis, bursitis, acute gout, and for management of pain and primary

dysmenorrhea. Naprosyn is to be given BID. The lower strength, naproxen sodium (Eqi. 200 mg) IR tablet, is also on the market as an over-the-counter (OTC) drug, "Aleve".

In a prior supplement, Prevacid was approved for the treatment of NSAID-associated gastric ulcer. TAP's NDA 21-507 submitted on 09/06/02 is seeking approval for copackaging of lansoprazole EC capsule and naproxen IR tablets. Each daily dose consists of one Prevacid 15 mg EC capsule and two Naprosyn IR tablets, either 250 mg (Naprapac 250), 375 mg (Naprapac 375) or 500 mg tablets (Naprapac 500). Naprapac 250, 375, or 500 is to be indicated for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, in patients with a history of a documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID, such as Naprosyn. A "Letter of Authorization" from Roche Laboratories was provided to TAP for cross-referencing to NDA 17-581 (Naprosyn).

No new human pharmacokinetic (PK) studies or clinical trials were conducted to support this NDA. The sponsor provided "Overall Human Pharmacokinetics Summary-Overview of the Drug-Drug Interaction (DDI) Potential Between Lansoprazole and Naproxen" which included a DDI study between omeprazole and naproxen from the literature to address the Agency's concern on the DDI potential between lansoprazole and naproxen. It is concluded that clinically significant DDI between lansoprazole and naproxen is unlikely. The dissolution data obtained from naproxen IR 250 and 500 mg tablet lots is acceptable.

The sponsor also submitted "Overall Clinical Summary" which contained a review of the subset of patients taking lansoprazole and naproxen-only from the previously submitted data that supported the use of lansoprazole for the treatment of NSAID-associated gastric ulcer. The results of these subset analyses of naproxen-only reportedly showed statistical significance for the risk reduction of NSAID-associated gastric ulcer with Prevacid 15 mg or 30 mg as compared to placebo. Both Prevacid EC 15 mg or 30 mg treatment group remained free from gastric ulcer significantly longer than placebo group ($p < 0.001$). However, no difference between Prevacid 15 and 30 mg treatment groups was found.

A. Recommendations

TAP's NDA 21-507 submitted on 09/06/02 for copackaging of Prevacid EC 15 mg capsule and Naprosyn (250, 375, or 500 mg IR tablets) has been reviewed by OCPB/DPE II. OCPB is of the opinion that the NDA is acceptable from OCPB perspective. The labeling comments (p. 7) need to be conveyed to the sponsor and incorporated into PI for revision.

05/22/03

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Suresh Doddapaneni, Ph.D. _____ 05/30/03

FT initialed by Suresh Doddapaneni, Ph.D. _____ 06/05/03

cc: NDA 21-507, HFD-180 (N. Nair, M. Furness), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski).

II. Table of Contents

	Page
I. Executive Summary	1
II. Table of Contents	3
III. Summary of CPB Findings	3
IV. QBR	4
V. Labeling Recommendations	7
VI. Appendices	7
1. Proposed labeling	
2. Filing and review form	

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

TAP's NDA 21-507 submitted on 09/06/02 is seeking approval for copackaging of one lansoprazole EC 15 mg capsule and two naproxen IR tablets either 250 mg (Naprapac 250), 375 mg (Naprapac 375), or 500 mg (Naprapac 500). Each daily dose consists of one Prevacid 15 mg EC capsule and two Naprosyn IR tablets, either 250 mg, 375 mg or 500 mg. The Prevacid capsule and one Naprosyn tablet are to be taken in the morning with a glass of water before eating and the second Naprosyn tablet in the evening with a glass of water.

Naprapac 250, 375, or 500 is proposed for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, in patients with a history of a documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID, such as Naprosyn. A "Letter of Authorization" from Roche Laboratories was provided to TAP for cross-referencing to NDA 17-581 (Naprosyn).

No new human PK studies were conducted to support this NDA. Upon a request made by the Agency in the pre-NDA meeting on 02/22/02, the sponsor submitted an "Overall Human Pharmacokinetics Summary-Overview of the Drug-Drug Interaction Potential Between Lansoprazole and Naproxen" to address the Agency's concern on the DDI potential between lansoprazole and naproxen. The sponsor provided a DDI study from the literature regarding omeprazole and naproxen. The results reportedly showed that after one-week dosing, omeprazole 20 mg EC capsule QD had no effect on the PK of naproxen 250 mg BID and that naproxen had no effect on the PK of omeprazole. Overall, clinically significant DDI between lansoprazole and naproxen is unlikely. Additional *in vitro* protein binding study also showed that no clinically significant interactions were observed. The dissolution data for the repackaged Naprosyn tablets met the approved dissolution specifications.

No new clinical trials were conducted. The sponsor, however, submitted a review of the subset of patients taking lansoprazole and naproxen-only from the previously approved Prevacid's NDA 20-408 Supplement No. 033 (clinical study No. M95-301). The results of these subset analyses of naproxen-only reportedly showed statistical significance for the risk reduction of NSAID-associated gastric ulcer with Prevacid 15 mg (n=37) or 30 mg (n=24) as compared to

placebo (n=30). Both Prevacid 15 mg or 30 mg treatment group remained free from gastric ulcer significantly longer than placebo group ($p < 0.001$). No difference, however, was found between Prevacid 15 and 30 mg treatment groups.

IV. Question Based Review

A. General Attributes

Lansoprazole is a PPI. Prevacid (lansoprazole) EC 15 and 30 mg capsules are currently on the market indicated for 1) short-term treatment of gastric or duodenal ulcers, 2) healing of NSAID-associated gastric ulcer, and 3) for symptomatic GERD. A dose of 15 or 30 mg is to be given QD before meals.

Naproxen is an NSAID. Naprosyn (naproxen) IR 250, 375, and 500 mg tablets are also currently on the market as prescription drug indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis and also for the treatment of tendonitis, bursitis, acute gout, and for management of pain and primary dysmenorrhea. It is to be given BID.

B. General Clinical Pharmacology

Under NDA 21-507, a copackaging of one lansoprazole EC 15 mg capsule and two naproxen IR tablets either 250 mg (Naprapac 250), 375 mg (Naprapac 375), or 500 mg (Naprapac 500) is to be indicated for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, in patients with a history of a documented gastric ulcer, who require risk reduction of gastric ulcers associated with the chronic use of an NSAID, such as Naprosyn.

C. Extrinsic Factors

Q: Could lansoprazole and naproxen show clinically significant DDI?

A: Clinically significant DDI is unlikely between lansoprazole and naproxen.

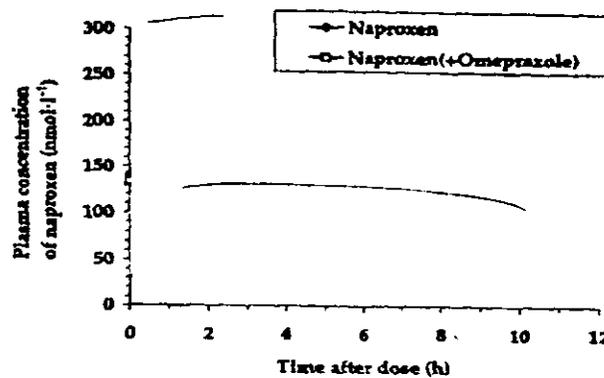
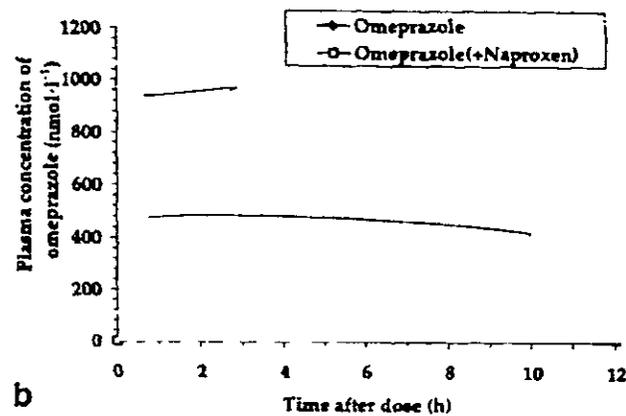
Specific DDI interaction potential between lansoprazole and naproxen has not been investigated. Upon a request made in the pre-NDA meeting, the following published DDI study between omeprazole and naproxen was submitted to show that DDI between lansoprazole and naproxen is unlikely.

“Lack of Drug-Drug Interaction Between Three Different NSAIDs and Omeprazole” by Andersson T. et al., Eur. J. Clin. Pharmacol. (1998) 54: 399-404

This was a study of three separate investigations in 24 healthy male and female subjects. In each investigation, omeprazole EC 20 mg capsule (Losec® of Astra, Sweden) and one of the three NSAIDs were given. Each investigation employed

an open-label, randomized, 3x3 crossover design with at least one-week washout period, i.e., 1) omeprazole QD for a week alone, 2) one of the NSAIDs alone [diclofenac 50 mg BID for a week, naproxen 250 mg tablet (Naproxen of Astra, Sweden) BID for a week, or piroxicam 10 mg QD for 10 days], and 3) omeprazole plus one of the NSAIDs. After fasting overnight, morning medication was given and standard meals were then provided at 4, 7, and 10 hrs postdose on the days of visit at the laboratory for blood sampling.

Sufficient blood samples were collected and plasma samples were analyzed for generating complete plasma profiles of omeprazole (up to 12 hrs) and each of 3 NSAIDs (also up to 12 hrs except for 24 hrs for ———). It was reported that 1) none of the NSAIDs had any effect on the peak plasma concentration (C_{max}) or plasma concentration vs. time (AUC) of omeprazole and 2) omeprazole had no significant influence on the PK of the NSAIDs. The DDI results between omeprazole 20 mg EC capsule QD and naproxen 250 mg tablet BID are shown below.



Therefore, the data in this article indicates that the absorption of naproxen is not pH dependent. Also, the metabolic pathways for lansoprazole (via CYP 2C19 and 3A4/5) and naproxen (via CYP 2C9 and 1A2) are different and both lansoprazole

and naproxen are not known to be inducers or inhibitors of CYP 450 enzymes. Additional *in vitro* protein binding study also showed that no clinically significant interactions between lansoprazole and naproxen were observed. The effects of lansoprazole on other NSAIDs, e.g., indomethacin, ibuprofen, and aspirin had been examined in previous "Drug Metabolism Report No. 32" for lansoprazole and no clinically significant effects were found. Overall, clinically significant DDI between lansoprazole and naproxen is unlikely.

D. General Biopharmaceutics

Each daily dose consists of one Prevacid 15 mg EC capsule and two Naprosyn IR tablets, either 250 mg, 375 mg or 500 mg. The Prevacid capsule and one Naprosyn tablet are to be taken in the morning with a glass of water before eating and the second Naprosyn tablet in the evening with a glass of water. Each convenience package of Naprapac (250, 375 or 500) contains sufficient product for seven days of treatment.

Q: Is a food effect study needed for the co-administration of lansoprazole EC 15 mg capsule and naproxen IR tablets?

A: The food effect study is not needed.

Lansoprazole EC capsule has been previously approved for healing of NSAID-associated gastric ulcer and it is instructed to take lansoprazole before meals in the package insert (PI) for lansoprazole. Furthermore, no instructions of giving individual drugs with food are stated in individual PI and in this proposed PI for copackaging product. Therefore, no food effect study is considered needed.

Dissolution:

Naprosyn tablet lots were manufactured and packaged at the Roche Lab. Inc. in Leganes, Spain. The dissolution data of Naprosyn 250 and 500 mg tablet lots (using the approved dissolution methodology) is summarized below:

Mean (\pm SD) Dissolution Data of Naprosyn 250 and 500 mg Tablet Lots for Initial Test on Stability

Strength	250 mg Tablets (n=6/lot)		500 mg Tablets (n=6/lot)			
	Lot No.	BN89327/1	BN89326	I-41 (940180)	I-43 (940225)	I-42 (940204)
Dissolution (Q= in 45min)		102 \pm 1	99.8 \pm 1.5	98.7 \pm 1.2	102 \pm 2	102 \pm 2

Although no testing results for the 375 mg tablet lots were submitted, the above dissolution data obtained from the above 250 mg and 500 mg tablet bracket the 375 mg strength. The dissolution data is adequate.

V. Labeling Recommendations

Please see Appendix 1 for OCPB labeling comments (double underline for addition and double strikethrough for deletion)

VI. Appendices

1. Proposed Package Insert (Original, 08/15/02 version), and OCPB Comments
2. OCPB Filing/Review Form

APPEARS THIS WAY
ON ORIGINAL

NDA 21-507 for Naprapac 250, 375, or 500

Appendix 1

Sponsor's Proposed Labeling (08/15/02 Version)

23 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

NDA 21-507 for Naprapac 250, 375, or 500

Appendix 2

OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-507	Brand Name	Naprapac 250, 375, and 500 (pending)
OCPB Division (I, II, III)	DPE II	Generic Name	Prevacid + Naprosyn
Medical Division	HFD-180	Drug Class	PPI + NSAID
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, in patients with a history of a documented gastric ulcer, who require risk reduction of gastric ulcer associated with the chronic use of an NSAID, such as Naprosyn (naproxen).
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	EC Capsules and IR Tablets
		Dosing Regimen	Prevacid 15 mg Capsule QD + Naprosyn 250, 375, or 500 mg Tablet BID
Date of Submission	09/06/02	Route of Administration	Oral
Estimated Due Date of OCPB Review	06/03/03	Sponsor	Tap Pharmaceuticals
Medical Division Due Date	06/04/03	Priority Classification	S
PDUFA Due Date	07/09/03		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:	X	1	1	All in one study
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Is there a concern on drug-drug interaction between Lansoprazole and Naproxen?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-507, HFD-850 (Electronic Entry or Lee), HFD-180 (N. Nair, M. Furness), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski), CDR (Z. Zadeng)

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Tien-Mien Chen
6/5/03 06:20:33 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/5/03 06:27:07 PM
BIOPHARMACEUTICS

RECEIVED BY FAX
ON ORIGINAL