CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22511Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FROM: Sushanta Chakder, Ph.D., Supervisory Pharmacologist

DATE: April 13, 2010

Application number: NDA 22,511

Date of submission: June 30, 2009

Sponsor: POZEN Pharmaceutical Development Co.

Drug Product: VIMOVO (Naproxen/Esomeprazole magnesium)

Indication: Treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis patients at risk of developing NSAID-associated gastric ulcer

Comments:

Under NDA 22511, the sponsor is seeking approval of a combination of naproxen and esomeprazole magnesium for the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis patients at risk of developing NSAID-associated gastric ulcer. The only nonclinical study submitted in this NDA application was a pharmacokinetic study in which the urinary and plasma metabolites of buffered and unbuffered omeprazole were determined in female Sprague Dawley rats following 14 days of oral dosing. The NDA was supported by reference to the Agency's previous findings of safety and publicly available information on the toxicology of naproxen and esomeprazole (including omeprazole) to meet the nonclinical assessment requirements.

The nonclinical safety of esomeprazole and naproxen has been established by the respective innovators. During approval of the espmeprazole (Nexium) application, its nonclinical safety was partially based on studies conducted with omeprazole. Following oral administration of omeprazole buffered and unbuffered formulation to female Sprague Dawley rats, the plasma and urinary metabolite profiles for omeprazole were similar. Thus, following oral administration of uncoated esomeprazole, present in VIMOVO, the patients are not expected to be exposed to any new metabolites. Since the mechanisms of action, and the microsomal enzyme systems involved in the metabolism the two components of VIMOVO are not similar, no significant drug-drug interactions between the two components are expected. The sponsor adopted the labeling of the nonclinical sections from the existing labeling of the individual components which is acceptable.

Recommendations:

1. I concur with Dr. Wu's recommendation that there are no additional nonclinical safety concerns for the proposed combination of naproxen and esomeprazole, other than those expected from the individual components.

2. In the nonclinical sections of the labeling (Sections 8.1 and 13.1), the sponsor used headings for reproductive toxicology and carcinogenicity studies of individual components of VIMOVO. These headings should be removed form the labeling.

3. From a nonclinical standpoint, the NDA application is approvable with the recommended changes in the labeling.

Sushanta Chakder, Ph. D. Date
Supervisory Pharmacologist, HDF-180

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22511	ORIG-1	POZEN INC	PN 400 NAPROXEN/ESOMEPRAZOLE MAGNESIUM

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/s/

SUSHANTA K CHAKDER
04/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22511
Supporting document/s:	1
Applicant's letter date:	June 30, 2009
CDER stamp date:	July 1, 2009
Product:	VIMOVO (naproxen/esomeprazole magnesium)
Indication:	Treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis patients at risk for developing NSAID-associated gastric ulcer
Applicant:	POZEN Pharmaceutical Development Co.
Review Division:	Gastroenterology Products
Reviewer:	Charles G. Wu, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Anna Simon, MSN, CPNP

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, approval of the NDA application is recommended.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

In this 505(b)(2) NDA submission, the sponsor did not submit any new nonclinical studies on Naproxen, Esomeprazole or the combination. The nonclinical sections of the labeling are adopted from the innovator's labeling of Naproxen and Esomeprazole. Therefore, no changes in the proposed labeling are recommended.

1.2 Brief Discussion of Nonclinical Findings

The sponsor did not submit any nonclinical study reports in this NDA except a PK study on determination of urinary and plasma metabolite profiles following 4 days oral administration of buffered- and unbuffered-omeprazole to female Sprague Dawley rats. In addition, the following statement was made: "This NDA is submitted under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act and relies on studies that were not conducted by or for the applicant and for which this applicant does not have right of reference. Specifically, this NDA is supported by reference to the Agency's previous findings of safety and publicly available information on the toxicology of naproxen and esomeprazole (including omeprazole) to meet the nonclinical assessment requirements as part of the PN 400 new drug application, by POZEN". In addition to the above-mentioned PK study, the sponsor provided published studies to support the safety of the drug from a nonclinical standpoint. Pharmacologic, pharmacokinetic and toxicological properties of individual components of PN 400 (naproxen and esomeprazole, including omeprazole) are well-established.

Like other non-steroidal anti-inflammatory drugs (NSAIDs), naproxen inhibits cyclooxygenase enzyme activity. This inhibition reduces prostaglandin synthesis and leukocyte activation resulting in anti-inflammatory, analgesic and anti-pyretic activity. Esomeprazole is a substituted benzimidazole that suppresses gastric acid secretion through specific inhibition of the

H^+, K^+-ATPase enzyme located in the secretory membrane of the gastric parietal cell. This enzyme is the acid (proton) pump within the gastric parietal cell. Hence, esomeprazole is a proton pump inhibitor (PPI). PPIs inhibit the final common pathway of acid production in the stomach and thus reducing both basal and stimulated gastric acid secretion.

Following oral administration, naproxen is almost completely absorbed with a bioavailability of approximately 95 to 99% in dogs, minipigs and humans, but only about 50% in rats. T_{max} values in animals range from 0.5 to 2 hours; similarly the T_{max} in humans usually occurs 1 to 2 hours after dosing. The half-life of naproxen in man is 10 to 17 hours, while rodents have a short half-life of 1 to 3 hours or less, but in dog with a prolonged half-life (35 to 74 hours). There are no consistent gender-related differences in naproxen pharmacokinetics and no apparent differences in exposure between pregnant and non-pregnant rats and rabbits. Tissue distribution studies in rats suggest that there is no preferential uptake of naproxen by any major organ system, which is consistent with its low volume of distribution (approximately 10% of body weight) and its high (98 to 99%) protein binding. Naproxen is extensively metabolized, with only 1% of the naproxen dose recovered in urine as the unchanged parent drug. Approximately 95% of an oral naproxen dose is recovered in urine, largely as the conjugated metabolites of naproxen and its O-demethylated metabolite (66 to 92% of the dose). Only 1 to 2% of a radioactive dose of naproxen is recovered in feces following intravenous administration. *In vitro* studies have demonstrated that CYP2C9 and CYP1A2 are the two primary CYP450 isoenzymes responsible for the oxidative metabolism of naproxen to form 6-O-desmethylnaproxen in humans and most animal species.
After oral dosing, omeprazole was rapidly absorbed in mice, rats and dogs and was readily distributed into tissues. T_{max} was 10, 15, 5 to 15 and 13.8 minutes in the mouse, rat, dog and human, respectively. The oral bioavailability was only about 5% in fed and 15 to 20% in starved rats of either sex. The C_{max} and AUC values were similar after treatment with equivalent oral doses of esomeprazole or omeprazole, but higher plasma concentrations of both compounds were noted in females compared to males. In dogs, exposure (AUC) after oral administration of the same dose of omeprazole and esomeprazole was equivalent, but the C_{max} value was somewhat higher after esomeprazole administration. There were no significant differences between single and repeated administration, or between males and females. Omeprazole was 87.5, 90 and 95.7% bound to plasma proteins in rat, dogs and humans, respectively. Both compounds were metabolized via the same biotransformation routes to the same primary metabolites. The *in vitro* metabolism studies by CYP enzyme system have shown that CYP2C19 is the key enzyme involved in the formation of the hydroxyl metabolite, a major metabolite of both esomeprazole and omeprazole. The formation of the achiral sulfone, another primary metabolite, is dependent on CYP3A4. The elimination half-lives in the rat, dog and man were approximately 60 minutes. The esomeprazole in PN 400 is immediate-release and therefore subject to acid degradation in the gastric lumen, which is different to the marketed delayed-release esomeprazole. In a study in rats (PN200-T1) submitted in this NDA, similar metabolite profiles were noted in rats given oral omeprazole either with or without buffer for 14 days. This indicates that there were no significant differences in the systemic exposure to any degradation products that may have been formed in the gastric lumen of rats given omeprazole with or without buffer.

No new nonclinical toxicology studies have been conducted by POZEN with PN 400 or a naproxen/esomeprazole combination. The principal findings after single and repeat-dose oral

naproxen administration in animals and humans are thought to be due to inhibition of prostaglandin synthesis; they include gastrointestinal irritation and renal injury. Regenerative anemia, increased extramedullary hematopoiesis, increased white blood cells (neutrophils) and decreased serum total protein and albumin occur secondary to the gastrointestinal erosions/ulcers and bleeding caused by naproxen. Increases in serum BUN and proteinuria also occur and correlate with naproxen-associated renal injury. Toxicology studies showed no genetic, reproductive, teratogenic or oncogenic adverse effects.
The acute toxicity of esomeprazole was low after both oral and IV administration to rats, and was equivalent to that of omeprazole. Besides lethality, the main signs of acute toxicity were unspecific neurological effects, changes in respiratory frequency and abdominal respiration. Repeated oral treatment of rats with esomeprazole or omeprazole at oral doses of 14-280 mg/kg/day for up to 3 months resulted in low systemic toxicity. In both rats and dogs, histopathological changes in the stomach, accompanied by a dose-dependent increase in stomach weight and serum gastrin levels, were noted at the higher dose levels of both compounds. Esomeprazole was not mutagenic in an Ames test, but was clastogenic in an *in vitro* human lymphocyte assay. Omeprazole, its R-enantiomer, also showed similar clastogenic activity under the same experimental conditions. In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 2 to 175 times the human dose of 40 mg per day, based on 50 kg body weight) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was higher in female rats, which show higher blood levels of omeprazole. Since no carcinoid-free dose was established for the female rats in this first study, a second 104-week carcinogenicity study was completed using female rats only. The second study also revealed a dose-related increase in the incidence of gastric carcinoids. Omeprazole at oral doses up to 138 mg/kg/day in rats was found to have no effect on fertility and reproductive performance and had no teratogenic potential. At the high dose level in rabbits, severe anorexia, reduced water consumption and reduced body weight was noted in the dams, but all animals survived, ate and gained weight as soon as dosing was stopped. Decreased litter size and increased fetal loss was noted in rabbits at both 69 and 138 mg/kg, with some minor fetal effects at 138 mg/kg due to maternal toxicity. An extended peri- and post-natal study with omeprazole in rats demonstrated only slight reductions in food consumption and body weight gain and a slight decrease in the mean body weight gain of the pups.

2 Drug Information

2.1 Drug: VIMOVO (naproxen/esomeprazole magnesium) Tablets

2.1.1 CAS Registry Number: Naproxen 22204-53-1,

Esomeprazole Magnesium 161973-10-0

2.1.2 Generic Name: Naproxen and Esomeprazole

2.1.3 Code Name: PN 400

2.1.4 Chemical Name:

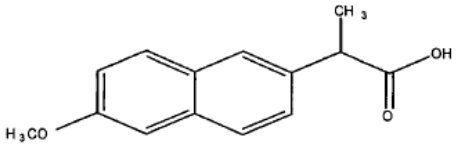
Naproxen - (S)-6-methoxy-α-methyl-2-napthaleneacetic acid
Esomeprazole magnesium - bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) Methyl] sulfinyl]-l*H*- benzimidazole-l-yl) magnesium trihydrate

2.1.5 Molecular Formula/Molecular Weight

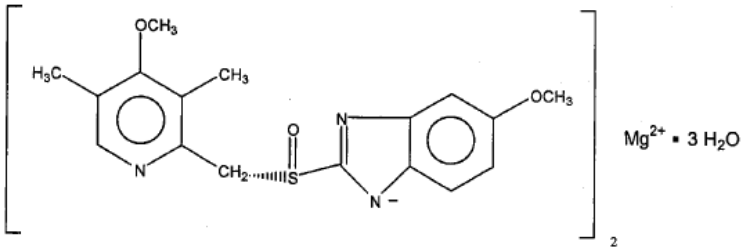
Naproxen: $C_{14}H_{14}O_3$/MW 230.26;
Esomeprazole: $(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$/MW 767.2

2.1.6 Structure

Naproxen - (*S*)-6-methoxy-α-methyl-2-napthaleneacetic acid



Esomeprazole magnesium – bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*- benzimidazole-1-yl) magnesium trihydrate



2.1.7 Pharmacologic class

Naproxen: NSAID (Non-Steroidal Anti-Inflammatory Drug)
Esomeprazole: PPI (Proton Pump Inhibitor)

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 76-301 for PN 400 (500 mg naproxen/ 20 mg esomeprazole magnesium) (b) (4) for the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients at risk for developing NSAID-associated gastric ulcers.

2.3 Clinical Formulation

2.3.1 Drug Formulation

500 mg of Naproxen with (b) (4) of Croscarmellose Sodium, (b) (4) of Povidone, (b) (4) of Colloidal Silicon Dioxide and 20 mg of Esomeprazole with (b) (4), (b) (4) of Methacrylic Acid Copolymer, film coated tablet.

2.3.2 Comments on Novel Excipients

No novel excipients are present in VIMOVO. None of the excipients used in the manufacture of VIMOVO Tablets are of animal origin.

2.3.3 Comments on Impurities/Degradants of Concern

Total impurities in naproxen are not more than (b) (4), and any individual impurity does not exceed (b) (4). Total impurities in esomeprazole are not more than (b) (4), and any individual impurity does not exceed (b) (4) for indentified or (b) (4) for any unidentified impurity. The individual impurities in both drugs are equal to the qualification thresholds as per ICH Q3B(R2), and are acceptable.

2.4 Proposed Clinical Population and Dosing Regimen

Proposed clinical population is patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis at risk for developing NSAID-associated gastric ulcers. Risk factors include age, documented history of gastric ulcers, or concomitant therapy with low dose aspirin.

2.5 Regulatory Background

To identify and characterize any new degradants that may arise from the administration of immediate-release omeprazole, which is different from the marketed delayed-release omeprazole, the Division asked the sponsor to conduct a PK study on determination of urinary and plasma metabolite profiles following 14-day oral administration of buffered- and

unbuffered-omeprazole, as support for a related product (PN200, (b) (4): naproxen 500 mg/omeprazole 20 mg). The study was submitted and reviewed.

3 Studies Submitted

3.1 Studies Reviewed

The Sponsor submitted a PK study on determination of urinary and plasma metabolite profiles following 14-day oral administration of buffered- and unbuffered-omeprazole to female Sprague Dawley rats. In addition, several published study reports were submitted in this submission and selected studies were reviewed.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Summaries of nonclinical studies under IND 76-301 for PN 400 (20 mg Esomeprazole/500 mg Naproxen) and (b) (4) for PN 200 (20 mg Omeprazole/500 mg Naproxen) (POZEN).

4.1 Primary Pharmacology

The following published pharmacology studies on naproxen and PPI were selectively reviewed:

Mechanisms of Nonsteroidal Anti-Inflammatory Drug-Induced Gastric Damage R. Schoen and R. Vender, the American J. of Medicine, 1989 86:449-458

The molecular pharmacology of naproxen is similar to that of other non-steroidal anti-inflammatory drugs (NSAIDs); all are cyclo-oxygenase inhibitors. The naproxen anion inhibits prostaglandin synthesis. The physiological effects of naproxen, like other NSAIDs, include anti-inflammatory, analgesic and anti-pyretic activity. These 3 therapeutic effects are due both to a reduction in prostaglandin synthesis and an inhibition of leukocyte activation. Naproxen is known to produce ulcers and erosions in the digestive tract of animals and humans. Concepts regarding NSAID-induced gastroduodenal mucosal injury have evolved from a simple notion of topical injury to theories involving multiple mechanisms with both local and systemic effects. According to the dual-injury hypothesis, NSAIDs have direct toxic effects on the gastroduodenal mucosa and indirect effects through decreased protective mucosal prostaglandins.

Nonsteridal anti-inflammatory drugs and gastropathy: The second hundred years. Wallace JL. (1997) Gastroenterology 112:1000-1016.

Direct effects of therapeutic levels of NSAIDs on the gastric mucosa include ion trapping (resulting in high intracellular NSAID concentrations), gastric epithelial cell swelling and lysis, and an inhibition of adenosine triphosphate (ATP) production (leading to an inability to regulate intracellular pH or maintain the integrity of the gastric epithelial cell barrier). NSAIDs also directly interact with the surface phospholipids to reduce the hydrophobicity of the mucosal gel layer, exposing the gastric epithelium to the harsh acidic environment of the stomach. Through the inhibition of prostaglandin production, NSAIDs reduce the protective secretion of bicarbonate ion by the gastric mucosa, reduce gastric epithelial cell proliferation and migration (thus inhibiting gastric repair mechanisms), reduce mucosal blood flow (reducing the ability of the gastric mucosa to disperse H^+ ion and therefore regulate pH), and reduce platelet aggregation (promoting the bleeding of pre-existing ulcers). Thus, NSAIDs inhibit the ability of the gastric mucosa to protect and repair itself from the effects of gastric acid. Among the most common of these are hemorrhagic gastric erosions, which are most often found in the corpus. These erosions usually heal within a few days and occur less frequently as NSAID use is continued due to phenomenon of gastric adaptation to NSAID ingestion. Duodenal ulcers can also be induced by NSAIDs.

Antisecretory Effect of Leminoprazole on Histamine-Stimulated Gastric Acid Secretion in Dogs: Potent Local Effect. S. Okabe et al. Jpn. J. Pharmacol. 69: 91-100 (1995)

Esomeprazole belongs to a class of anti-secretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion through specific inhibition of the H+, K+-ATPase enzyme located in the secretory membrane of the gastric parietal cell. This enzyme is the acid (proton) pump within the gastric parietal cell. Hence, esomeprazole is characterized as a PPI. PPIs act to inhibit the final common pathway of acid production in the stomach and thus inhibit both basal and stimulated gastric acid secretion. Stimuli for gastric acid secretion include gastrin from the antral G cells, histamine from enterochromaffin-like cells in the gastric mucosa and acetylcholine via vagus nerve stimulation.

To determine whether or not systemic or local administration of a PPI exerts an antisecretory effect, the following study was conducted in conscious dogs. The gastric acid secretion by dogs with a vagally denervated Heidenhain pouch was stimulated by intravenous histamine infusion. Leminoprazole, a novel acid pump inhibitor, and omeprazole (as a reference drug) were administered either intravenously or locally into the pouch before or after histamine infusion. A bolus intravenous administration of leminoprazole and omeprazole significantly and dose-relatedly inhibited the stimulated gastric acid secretion for >26 hr. Local application of leminoprazole, but not omeprazole, significantly inhibited the acid secretion when applied for 15 to 30 min. The duration of the local antisecretory effect observed after 30 min application was around 8 - 10 hr. The acid-degraded products of leminoprazole had no effect when applied to the pouch. The blood concentration of leminoprazole was very low at 1 hr after local application. These results indicate that leminoprazole suppresses the secretory function of the parietal cells of dogs.

No nonclinical pharmacology studies have been conducted by POZEN with PN 400 or a naproxen / esomeprazole combination.

4.2 Secondary Pharmacology

No secondary pharmacology studies were submitted.

4.3 Safety Pharmacology

No studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No preclinical pharmacokinetic studies have been performed by POZEN with PN 400 or a naproxen / esomeprazole combination. (b) (4) POZEN completed study PN200-T1 in rats to identify and characterize any new degradants that may arise from the administration of immediate-release omeprazole. Qualitatively similar metabolite profiles in groups of animals treated with buffered or unbuffered omeprazole in this study indicated that there were no significant differences in the systemic exposure to any degradation products that may have been formed in the gastric lumen of rats given omeprazole with or without buffer.

Title: Determination of urinary and plasma metabolite profiles following 14-day oral administration of [^{14}C]omeprazole to female Sprague Dawley rats (Study # PN200-T1)

Methods: This degradant study was conducted to compare urine and plasma metabolite profiles from rats treated with ^{14}C-omeprazole ([^{14}C]OMZ) in buffered vs. unbuffered solutions used radioactive [^{14}C]-omeprazole. Groups of six female Sprague-Dawley (SD) rats each received 14 successive daily oral doses of ~128 mg/kg OMZ (Target: 138 mg/kg) containing [^{14}C]OMZ in buffered (5.1 mg/mL $NaHCO_3$ in 0.5% HPMC [pH 9.0]) or non-buffered (0.5% HPMC [pH 7.0]) suspensions. The radiochemical content of [^{14}C]OMZ doses was ~38 μCi (Target: 50 μCi). On Study Days 1, 4, 7, and 14, blood was sampled at 45 and 120 min post dose and plasma prepared. These time points were chosen based on data from a pilot study; the C_{max} for plasma radioactivity occurred at approximately 45 min and 120 min was the time when plasma metabolite recovery was highest. Daily urine and feces were collected separately at 0–8 and 8–24 h (urine) and 0−24 h (feces) intervals post dose and total radiochemical content determined. Metabolite profiles of urine and plasma collected on Study Days 1, 4, 7, and 14 were determined using HPLC radiochromatographic methods optimized during pilot studies. Total daily radiochemical recovery was determined. New degradants were identified by their consistent appearance in plasma and/or urine from rats treated with OMZ in an unbuffered solution relative to their consistent absence in plasma and/or urine from rats treated with OMZ in a buffered solution.

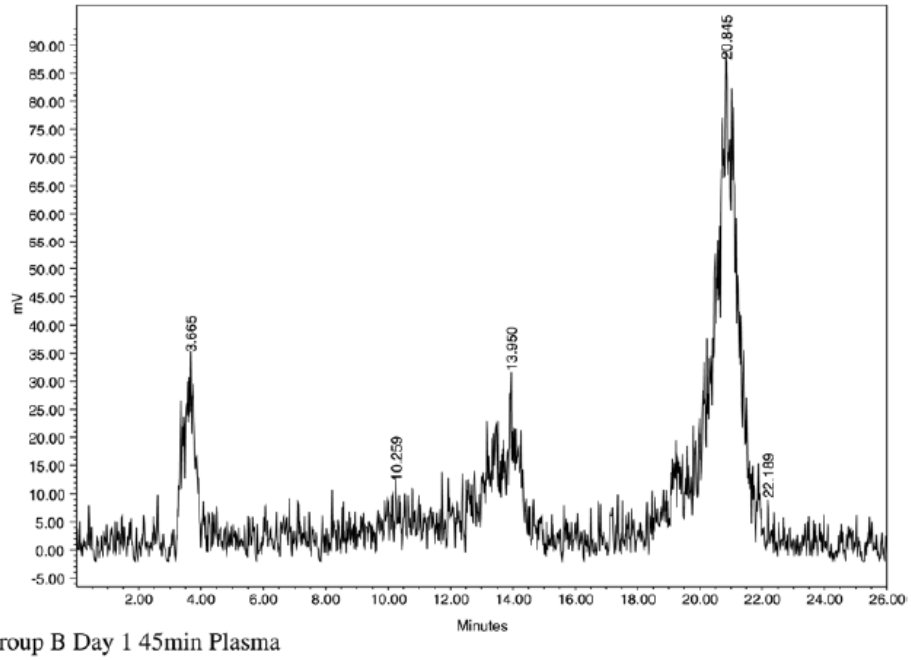
Results: Overall mean daily recovery of OMZ derived radioactivity was 78.4 ± 21.1% in rats receiving unbuffered formulations (Group A) and 88.4 ± 20.6% in rats receiving buffered formulations (Group B). All animals from both formulation groups showed signs of struggling

against dosing by Day 7 and study animals continued to struggle against dosing for the remainder of the study. Overall, Urinary elimination of OMZ derived radioactivity in the urine was similar between rats in the unbuffered group (Group A) relative to those in the buffered group (Group B). Group A urinary elimination of OMZ equivalents was 39.4 ± 6.5% on Day 1 of dosing and 27.0 ± 3.6% by Day 14. Group B urinary elimination of OMZ equivalents was 54.3 ± 2.0% on Day 1 of dosing and 35.9 ± 6.6% by Day 14. Fecal elimination of OMZ derived radioactivity was similar between rats in unbuffered group (Group A) relative to those in the buffered group (Group B). Group A mean fecal elimination of OMZ equivalents was 33.9 ± 11.5% on Day 1 of dosing and 56.9 ± 13.1% by Day 14. Group B fecal elimination of OMZ equivalents was 38.9 ± 7.1% on Day 1 of dosing and 60.4 ± 9.3% by Day 14. Generally the concentration of [^{14}C]OMZ derived equivalents in blood at 45 min and 2h post dose on Days 1, 4, 7, and 14 was higher in rats receiving OMZ in the buffered formulation (Group B) relative to those receiving OMZ in the unbuffered formulations (Group A). By Day 14, blood concentrations of [^{14}C]OMZ derived equivalents increased approximately 3 fold relative to those measured on Day 1 in both formulation groups. The concentrations of [^{14}C]OMZ derived equivalents in plasma at 45 min and 2 h post dose on Day 1were higher in rats receiving OMZ in the buffered formulation (Group B) relative to those receiving OMZ in the unbuffered formulations (Group A). In both formulation groups, the concentration of [^{14}C]OMZ derived equivalents in plasma was highest on Day 1, declined by ~40 − ~70% by Day 4, and then remained at those levels through Day 14. Plasma concentrations of [^{14}C]OMZ derived equivalents were similar between both formulation groups from Day 4 through Day 14.

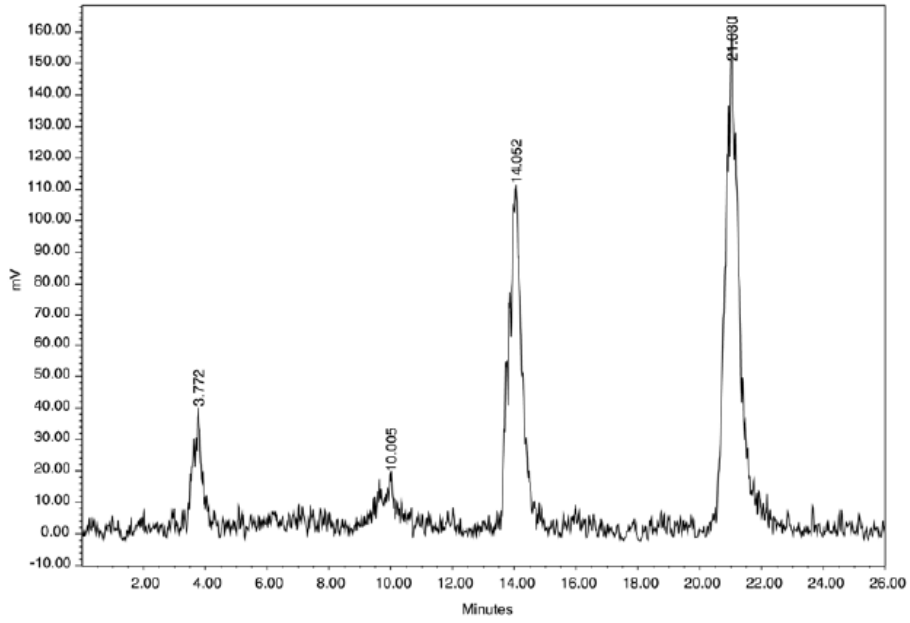
Metabolite profiles of rat plasma collected at 45 and 120 min following oral administration of [^{14}C]OMZ on Dose Days 1, 4, 7, and 14 consisted of several metabolites and parent OMZ. Representative HPLC radiochromatograms of plasma sampled from rats receiving either the unbuffered (Group A) or buffered (Group B) formulation of OMZ are displayed in Figures 1−2. Profiles of plasma metabolites varied between individual animals, but generally were qualitatively similar between rats receiving either the unbuffered (Group A) or buffered (Group B) formulation of OMZ on any given sampling time or day.

Figure 1. Representative HPLC Radiochromatograms of [^{14}C]OMZ-derived Metabolites in Plasma in Female SD Rats Receiving Unbuffered Formulations (Group A) and Buffered Formulations (Group B) of [^{14}C]OMZ Via Oral Gavage for 14 days: Day 1, 45 Minutes

Group A Day 1 45min Plasma

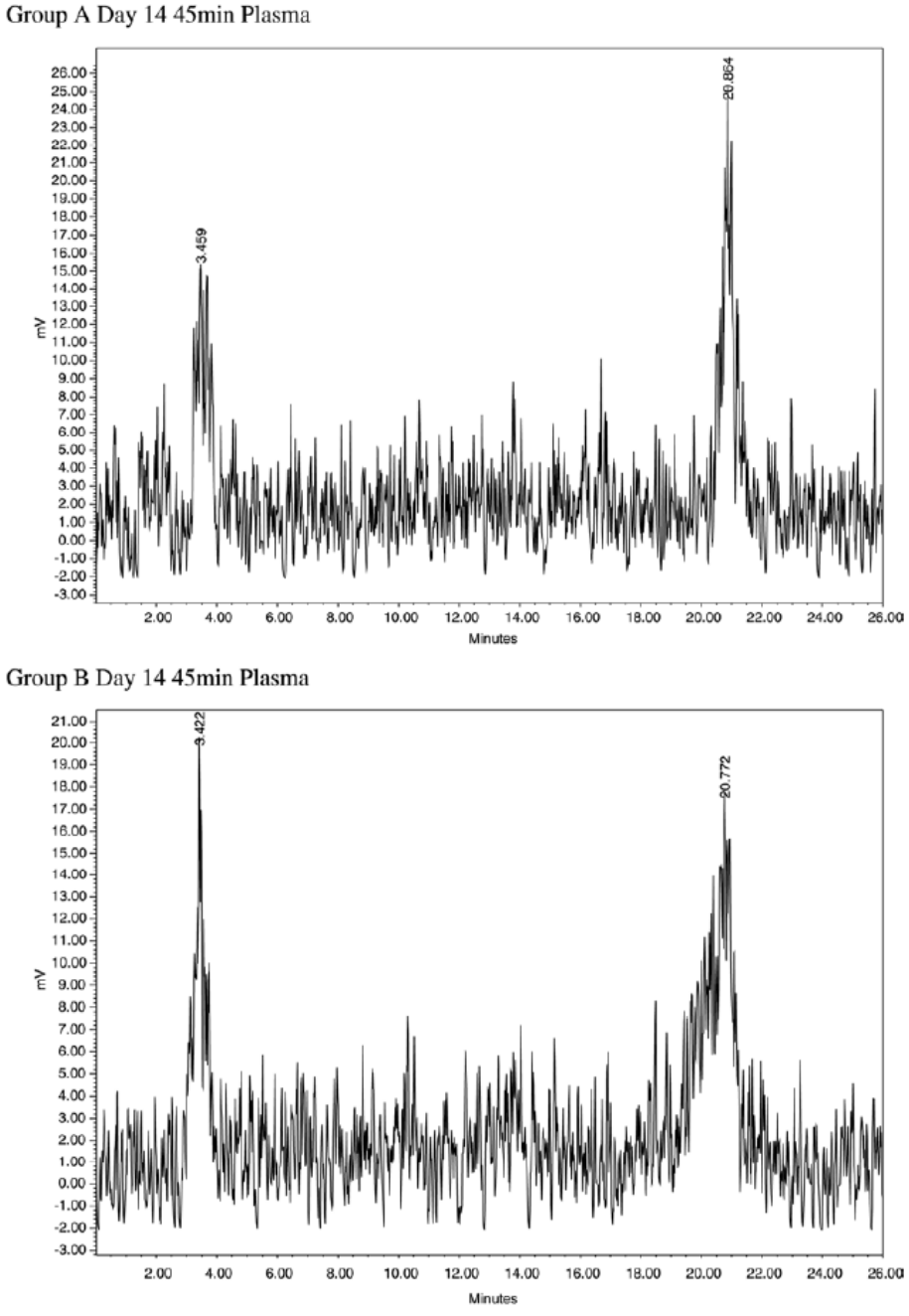


Group B Day 1 45min Plasma



As shown in the Fig 1, there were four metabolites (Relative Mean Total Area of 1.27, 0.25, 0.95 and 3.4 at Relative Retention Time of 0.17, 0.48, 0.68 and 1.00 respective) detected in plasma of individual rats receiving unbuffered formulation (Group A) on Day 1 which were also detected in the corresponding Day 1 Group B plasma samples with Relative Mean Total Area of 1.2, 0.36, 2.08 and 4.64. Similarly, there were two metabolites (Relative Mean Total Area of 0.35 and 0.349 at Relative Retention Time of 0.17 and 1.00 respective) detected in plasma of individual rats receiving unbuffered formulation (Group A) on Day 14 which were also detected in the corresponding Day 14 Group B plasma samples with Relative Mean Total Area of 0.39 and 0.57 as shown in Fig. 2.

Figure 2. Representative HPLC Radiochromatograms of [^{14}C]OMZ-derived Metabolites in Plasma in Female SD Rats Receiving Unbuffered Formulations (Group A) and Buffered Formulations (Group B) of [^{14}C]OMZ Via Oral Gavage for 14 days: Day 14, 45 Minutes

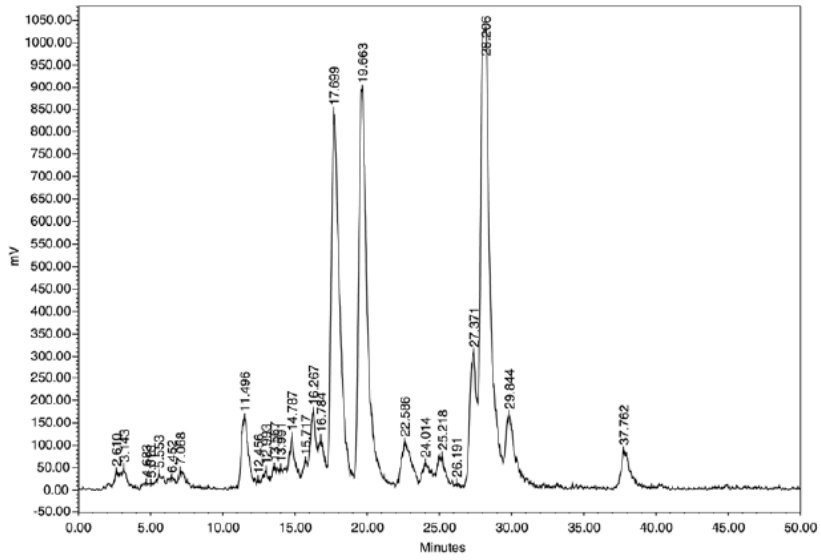


Metabolite profiles of rat urine collected at 0−8 and 8−24 h following oral administration of [^{14}C]OMZ on Dose Days 1, 4, 7, and 14 consisted of several metabolites. Parent compound

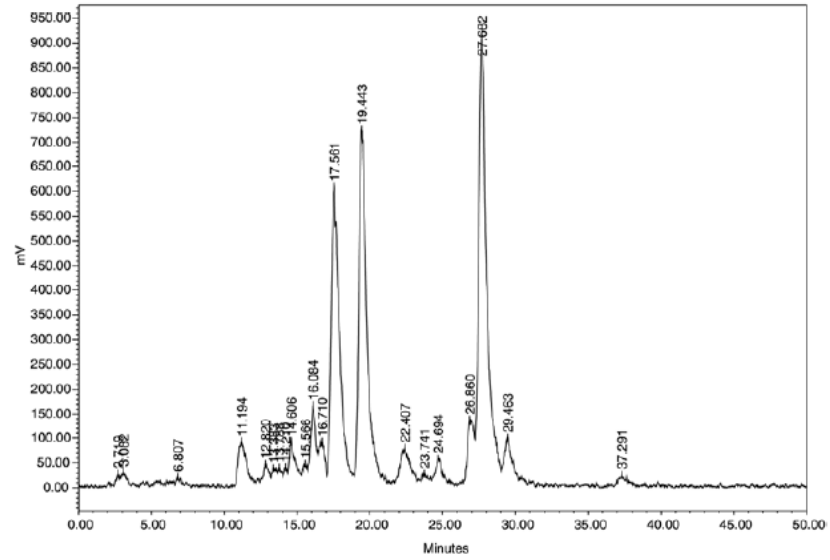
OMZ was detected in some but not all urine samples in this study. Representative HPLC radiochromatograms of urine sampled from rats receiving either the unbuffered (Group A) or buffered (Group B) formulation of OMZ are displayed in Figures 3-4. Profiles of metabolites in urine varied between individual animals but generally were qualitatively similar between rats receiving either the unbuffered (Group A) or buffered (Group B) formulation of OMZ dose on a given sampling time or day.

Figure 3. Representative HPLC Radiochromatograms of [^{14}C]OMZ-derived Metabolites in urine of Female SD Rats Receiving Unbuffered Formulations (Group A) and Buffered Formulations (Group B) of [^{14}C]OMZ Via Oral Gavage for 14 days: Day 1, 0-8 h collection

Group A Day 1 8h Urine



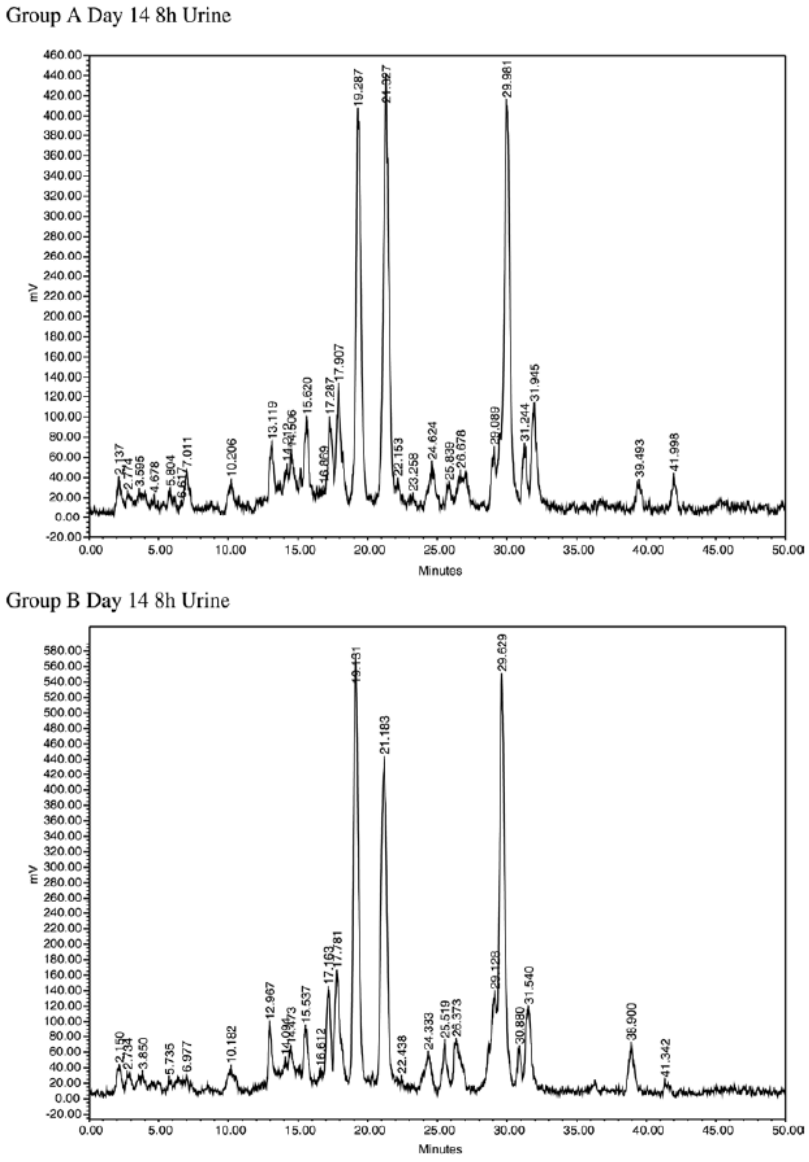
Group B Day 1 8h Urine



As shown in the Fig 3, there was a similar metabolite profile with 3 major metabolites (Relative Mean Total Area of 18.5, 17.8 and 24.7 at Relative Retention Time of 0.90, 1.00 and 1.42

respective) detected in urine of individual rats receiving unbuffered formulation (Group A) on Day 1 which were also detected in the corresponding Day 1 Group B urine samples with Relative Mean Total Area of 24.3, 26 and 34.2. Likewise, there were three major metabolites (Relative Mean Total Area of 8.65, 9.79 and 7.72 at Relative Retention Time of 0.91, 1.00 and 1.41, respectively) detected in urine of individual rats receiving unbuffered formulation (Group A) on Day 14 which were also detected in the corresponding Day 14 Group B urine samples with Relative Mean Total Area of 12.6, 12.5 and 12.48 as shown in Fig. 4.

Figure 4. Representative HPLC Radiochromatograms of [^{14}C]OMZ-derived Metabolites in urine of Female SD Rats Receiving Unbuffered Formulations (Group A) and Buffered Formulations (Group B) of [^{14}C]OMZ Va Oral Gavage for 14 days: Day 1, 0-8 h collection



In summary, plasma or urine metabolites were consistently detected in rats receiving unbuffered formulations of OMZ for 14 days that were also detected in the plasma or urine of rats receiving the buffered formulations of OMZ with identical metabolite profiles in this study.

Naproxen is a 2-arylpropionic acid nonsteroidal anti-inflammatory drug. The pharmacokinetics and metabolism of naproxen have been characterized and described in the literature and in the labeling of naproxen containing drug products and are reviewed below:

Absorption, distribution, metabolism and excretion of naproxen in various laboratory animals and human subjects. Runkel R, Chaplin M, Boost G, Segre E, and Forchielli E. (1972a) Journal of Pharmaceutical Sciences 61(5):703-708.

The comparative absorption, distribution, metabolism, and excretion of naproxen were studied in the rat, dog, guinea pig, monkey, minipig and also in human. Blood, urine, and fecal analyses were performed on specimens collected at several times after either oral ingestion or rapid intravenous administration of a radioactive dose.

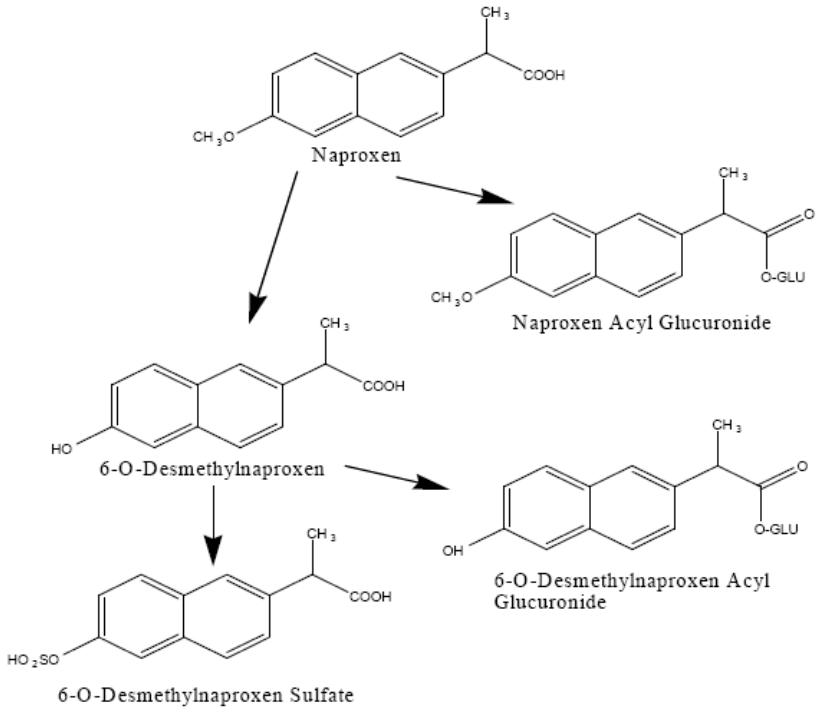
Following oral administration, naproxen is almost completely absorbed and undergoes minimal first-pass metabolism, with an absolute oral bioavailability of approximately 95 to 99% in dogs, minipigs and humans, but only about 50% in rats. T_{max} values in animals range from 0.5 to 2 hours; similarly the T_{max} in humans usually occurs 1 to 2 hours after dosing. The half-life of naproxen in man is 10 to 17 hours, while rodents have a short half-life of 1 to 3 hours or less. The pharmacokinetics of naproxen in the dog was markedly different from all the other species, with a prolonged half-life (35 to 74 hours) due enterohepatic recirculation. This may correlate with the high sensitivity of the dog to naproxen-induced GI ulceration. The species closest to humans in this aspect is the guinea pig, with a half-life of 9 hrs. Tissue distribution studies in rats suggest that there is no preferential uptake of naproxen by any major organ system, which is consistent with its low volume of distribution (approximately 10% of body weight) and its high (98 to 99%) protein binding. Naproxen C_{max} and, to a lesser extent, AUC values in all species generally increase linearly at low to mid dose levels (i.e., up to approximately 500 mg in human subjects), and less than dose proportionally at higher doses. Increased clearance of the drug at higher doses is secondary to saturation of plasma protein binding resulting in more unbound drug available for clearance. There are no consistent gender-related differences in naproxen pharmacokinetics and no apparent differences in exposure between pregnant and nonpregnant rats and rabbits. Naproxen reaching the systemic circulation is extensively metabolized, with only 1% of the naproxen dose recovered in urine as the unchanged parent drug. Approximately 95% of an oral naproxen dose is recovered in urine, largely as the conjugated metabolites of naproxen and its O-demethylated metabolite (66 to 92% of the dose). Only 1 to 2% of a radioactive dose of naproxen is recovered in feces following intravenous administration. The exception is the dog where the preferred route of elimination is through the feces, consistent with the extensive enterohepatic recirculation known to occur in this species.

Pharmacokinetics of naproxen, its metabolite O-desmethylnaproxen, and their acyl glucuronides in humans. Vree TB, van den Biggelaar-Martea M, Verwey-van Wissen CPWGM, Vree JB, and Guelen PJM. (1993) Biopharmaceutics and Drug Disposition 14:491- 502.

The primary metabolic pathway for naproxen is the Phase II conjugative metabolism, i.e., glucuronidation on the acyl moiety of naproxen. Approximately 51% of an oral dose of naproxen is recovered in urine as the acyl glucuronide plus an additional 7% as its isomerised conjugate

isoglucuronide. Naproxen also undergoes Phase I CYP450 mediated oxidative demethylation to form 6-O-desmethylnaproxen, which is further metabolized extensively via conjugation to 6-O-desmethylnaproxen acyl glucuronide (14% of the oral dose), its respective isoglucuronide (7% of the oral dose) and 6-O-desmethylnaproxen sulfate. The remaining dose recovered in urine has been attributed to the sulfate conjugate of 6-O-desmethylnaproxen, which was not measured in the relevant literature studies, and to unchanged naproxen and 6-O-desmethylnaproxen. The overall metabolic scheme of naproxen is shown in the figure below:

Figure 5. Metabolic Pathways of Naproxen



5.2 Toxicokinetics

None

6 General Toxicology

No toxicology studies have been conducted by POZEN with PN 400 or the naproxen/esomeprazole combination. Publicly available information on the toxicology of naproxen and similar information for esomeprazole obtained from the literature are summarized below.

6.1 Single-Dose Toxicity

Comparative toxicology of naproxen. Hallesy DW, Shott LD, Hill R. (1973)

Scandinavian Journal of Rheumatology Suppl 2:20-28.

The oral median lethal dose (LD_{50}) of naproxen varied substantially by species and administration route (vide infra). There were no significant differences in toxicity between male and female animals, and the wide range of findings in the rat appears to be due, at least in part, to different observation periods, strains, and laboratory facilities. The LD_{50} was 1300 mg/kg (mouse), 269 to >1000 mg/kg (rat) and 4,100 mg/kg (hamsters), with signs of CNS stimulation (tremors, convulsions), decreased activity and body weight, pallor, delayed bloody diarrhea and intestinal perforation. Acute lethality was attributed to CNS effects, whereas delayed deaths were considered due to GI erosions/ulcers. In dogs, the oral LD_{50} of naproxen was about 1 g/kg. Findings in the dog included GI irritation (inflammation, ulceration, bleeding, perforation and peritonitis) and CNS stimulation or depression. The intravenous LD_{50} of naproxen in mice was 455 mg/kg in one study and 528 mg/kg in another, with clinical signs similar to those seen after oral administration.

6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies were submitted. A summary of repeat-dose toxicity studies is provided below.

The primary toxicity of Naproxen that occurred in the 28-day range-finding study (POZEN, 2005 - Study MT400- T02) and definitive 90-day mouse study (POZEN, 2005 - Study MT400-T19) involved the pyloric region of the glandular stomach (and to a lesser extent, the duodenum) and was characterized by erosions and ulcers accompanied by inflammation and glandular hyperplasia in animals administered high-dose naproxen alone. No deaths occurred in rats at oral doses of up to 35 mg/kg/day naproxen administered for up to 28 days (POZEN, 2005 - Study MT400- T04). Mild reductions in red blood cell count, hemoglobin and hematocrit and increased mean corpuscular volume and reticulocytes (regenerative anemia) occurred as a result of hemorrhage into the GI tract; the existence of a mild regenerative anemia was further supported by findings of increased absolute and relative liver and spleen weights which correlated with compensatory increased erythroid extramedullary hematopoiesis in these organs. Abdominal adhesions and peritonitis occurred at ulcerogenic doses of naproxen, and the naproxen-induced GI inflammation was associated with myeloid hyperplasia of the sternal and/or femoral bone marrow. Hyperplasia was present in the mandibular and/or mesenteric lymph nodes in response to the injury and inflammation that occurred in the GI tract. The GI pathology was also associated with increased circulating platelets, white blood cells and neutrophils, reductions in serum albumin, albumin/globulin ratio and total protein and increased serum cholesterol. Renal tubular dilatation and regeneration occurred at naproxen doses of >75 mg/kg/day in the 28-day mouse study (POZEN, 2005 - Study MT400-T02), and were accompanied by increases in serum phosphorous and potassium. Similar renal degenerative changes were observed in a 13-week repeat dose study in rats (POZEN, 2003 - Study MT100-T04) and in the 2-year carcinogenicity study with naproxen. There was no evidence of a naproxen-induced effect on the kidney in the 90-day mouse study (POZEN, 2005 - Study MT400-TI9).

Repeated oral treatment of rats with esomeprazole or omeprazole at oral doses of 14-280

mg/kg/day for up to 3 months resulted in low systemic toxicity. In both rats and dogs, histopathological changes in the stomach (a dose-dependent chief cell eosinophilia in rats or atrophy, mucosal hyperplasia or fibrosis and/or focal necrosis of the gastric glands in dogs), accompanied by a dose-dependent increase in stomach weight and serum gastrin levels, were noted at the higher dose levels of both compounds. These changes were a result of gastrin stimulation and/or inhibition of gastric acid secretion. Except for the findings in GI tract, the 3-month toxicology studies in rats and dogs provided adequate safety margins for the clinical dose of 20 mg BID, 40 mg/day.

7 Genetic Toxicology

No genetic toxicology studies were conducted by sponsor. A summary of genetic toxicology studies is provided below:

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Naproxen and Esomeprazole were not mutagenic in bacterial systems (Ames assay).

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Naproxen was positive in a mutagenicity assay in mammalian cells, the *in vitro* mouse lymphoma assay (POZEN, 2003 - Study MT100- T25) and in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells, both in the absence and presence of an exogenous metabolic activation system (POZEN, 2005 - Study MT400-T07).

Esomeprazole was clastogenic in an *in vitro* human lymphocyte chromosome aberration assay.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Esomeprazole was not clastogenic in an *in vivo* mouse micronucleus test and an *in vivo* chromosome aberration test in rats. Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay.

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

Naproxen:

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/m^2). The maximum dose used yielded

0.28 times the systemic exposure to humans at the recommended dose (POZEN, 2003 - Study MTI 00- T37). No evidence of tumorigenicity was found.

Omeprazole:

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was higher in female rats, which had higher blood levels of omeprazole. Since no carcinoid-free dose was established for the female rats in this first study, a second 104 week carcinogenicity study was completed using female rats only. The second study also revealed a dose-related increase in the incidence of gastric carcinoids. No carcinoids were found in the mouse carcinogenicity study over 18-months at doses up to 140.8 mg/kg/day or in dogs following administration of 0.17 mg/kg/day of omeprazole for 7 years.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Reproduction studies with naproxen have been performed in rats at 20 mg/kg/day and mice at 170 mg/kg/day with no evidence of impaired fertility or harm to the fetus due to the drug as described in NAPROSYN® package insert.

Omeprazole at oral doses up to 138 mg/kg/day in rats was found to have no effect on fertility and reproductive performance.

9.2 Embryonic Fetal Development

Comparative toxicology of naproxen. Hallesy DW, Shott LD, Hill R. (1973) Scandinavian Journal of Rheumatology Suppl 2:20-28.

In developmental toxicity studies of Naproxen using Sprague-Dawley rats at daily doses up to 30 mg/kg and New Zealand White rabbits at up to 40 mg/kg, the only changes observed were a decrease in the number of live fetuses, with a concomitant increase in the number of dead fetuses and resorptions for some females in the high dose group. No visceral or skeletal abnormalities were observed in pups born to these animals.

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day and in pregnant rabbits at doses up to 69.1 mg/kg/day did not disclose any evidence for a teratogenic potential of omeprazole. Embryofetal toxicity was characterized by decreased litter sizes and increased fetal losses in the higher dose groups, especially in rabbits.

9.3 Prenatal and Postnatal Development

Comparative toxicology of naproxen. Hallesy DW, Shott LD, Hill R. (1973) Scandinavian Journal of Rheumatology Suppl 2:20-28.

When rats given daily oral dose of up to 30 mg/kg of naproxen, the only changes found were dystorcia or difficulties during parturition in 2/22 rats given 2mg/kg, 6/18 rats given 10 mg/kg, 4/22 rats given 20 mg/kg and 9/13 rats given 30 mg/kg of naproxen. Thus, the rat studies with Naproxen, drug known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition was observed.

A peri- and postnatal study with omeprazole in rats demonstrated only slight reductions in food consumption and body weight gain and a slight decrease in the mean body weight gain of the pups.

10 Special Toxicity Studies

None

11 Integrated Summary and Safety Evaluation

The sponsor did not provide any nonclinical study report in this NDA except for a PK study. Instead, this NDA was submitted under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act and relies on studies that were not conducted by or for the applicant and for which this applicant does not have right of reference. Specifically, the NDA is supported by reference to the Agency's previous findings of safety and publically available information on the toxicology of naproxen and esomeprazole (including omeprazole) to meet the nonclinical assessment requirements as part of the PN 400 new drug application. In this submission, the sponsor has submitted a PK study and provided published studies to support the safety of the drug from a nonclinical standpoint.

PN 400 is an oral fixed-dose combination product composed of a naproxen (marketed in the US since 1976, and is currently available as naproxen or naproxen sodium under the brand names of NAPROSYN®, EC-NAPROSYN®, ANAPROX® , approved for the management of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis) core covered by a layer of esomeprazole (marketed in the US since 2000 as NEXIUM®, approved for treatment of gastroesophageal reflux disease, treatment of patients with *H. pylori* infection and concurrent duodenal ulcer, and risk reduction of NSAID-associated gastric ulcers). Each PN 400 tablet contains 500 mg of delayed-release naproxen and 20 mg of immediate-release esomeprazole (present as 22.3 mg esomeprazole magnesium trihydrate salt). The sponsor is seeking indications for PN 400 for the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in patients who are at risk of developing NSAID associated gastric ulcers. Thus, there is no more new indication applied for the NDA other than those from each individual drug.

Naproxen is known to inhibit cyclooxygenase enzyme activity. This inhibition reduces prostaglandin synthesis and leukocyte activation resulting in anti-inflammatory, analgesic and

anti-pyretic activity. Esomeprazole is a substituted benzimidazole that suppresses gastric acid secretion through specific inhibition of the H^+, K^+-ATPase enzyme located in the secretory membrane of the gastric parietal cell. This enzyme is the acid (proton) pump within the gastric parietal cell. Hence, esomeprazole is characterized as a gastric proton pump inhibitor. The two components in PN 400 exert their pharmacological activity through very specific and quite different mechanisms. It is therefore not anticipated that there will be any direct and/or adverse pharmacological interaction between these two compounds. On the contrary, it is considered that the acid secretion inhibition resulting from treatment with esomeprazole will reduce the occurrence of the upper GI complications associated with naproxen therapy.

Neither naproxen nor esomeprazole should have any effect on the absorption or metabolism of the other drug. The ADME of the individual components of PN 400 have been well-characterized in both animals and man. Systemic exposures in clinical studies with PN 400 were bioequivalent with or similar to those for naproxen and esomeprazole when given separately, respectively; hence, there are no significant PK interactions and human systemic exposures are appropriately covered by existing nonclinical studies for these marketed drugs. CYP2C9 and CYP1A2 are the two primary CYP450 isoenzymes responsible for the oxidative metabolism of naproxen, whereas CYP2C19 and CYP3A4 are two key primary enzymes involved in the formation of the hydroxyl metabolite and the formation of the achiral sulfone for esomeprozole, respectively. The esomeprazole in PN 400 is immediate-release and therefore subject to acid degradation in the gastric lumen, which is different to the marketed delayed release esomeprazole. In a study in rats (PN200-T1) submitted in this NDA, qualitatively similar metabolite profiles were noted in rats given omeprazole either with or without buffer. This indicates that there were no significant differences in the systemic exposure to any degradation products that may have been formed in the gastric lumen of rats given omeprazole with or without buffer.

Based on a review of the data, combined administration of naproxen with esomeprazole is expected to demonstrate the known toxicity of each of the components; no new types of toxicity or exacerbation of existing toxicities should result from their combined administration. For a combination of these two compounds, the types, frequency and severity of adverse effects are likely to be characteristic of the toxicity of the major component, naproxen. The principal findings after single and repeat-dose oral naproxen administration in animals and humans are thought to be due to inhibition of prostaglandin synthesis; they include gastrointestinal irritation (inflammation, ulceration, bleeding, perforation and peritonitis) and renal injury (interstitial nephritis, papillary necrosis).

Use of naproxen and esomeprazole, alone or in combination, should be avoided during pregnancy (particularly late pregnancy) to be consistent with current product labeling for naproxen. Proposed labeling will reflect the appropriate subsections on nonclinical safety assessments and findings from the approved labeling of the respective components of PN 400.

The safety of the individual components of VIMOVO, naproxen and esomeprazole has been established in preclinical toxicology studies conducted by the innovators. Thus, the sponsor's proposed clinical doses for the proposed indications appear to be safe.

From a nonclinical standpoint, approval of the NDA application is recommended.

12 Appendix/Attachments

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22511	ORIG-1	POZEN INC	PN 400 NAPROXEN/ESOMEPRAZOLE MAGNESIUM

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

/s/

CHARLES G WU
03/17/2010

SUSHANTA K CHAKDER
03/17/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22511 **Applicant: Pozen** **Stamp Date: 6-30-09**

Drug Name: VIMOVO **NDA/BLA Type:505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A. No pharmacology/toxicology study was submitted. The applicant provided only the published literatures.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		See comment above
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	N/A		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		x	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Charles Wu 8/19/09

Reviewing Pharmacologist Date

Sushanta Chakder 8/19/09

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

CHARLES G WU
08/19/2009

SUSHANTA K CHAKDER
08/19/2009