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Prevacid® NapraPAC™ Monograph

Brand Name: Prevacid® NapraPAC™ 500

Generic Name: Naproxen/Lansoprazole

Manufacturer: Takeda Pharmaceuticals

Year Introduced: November 14, 2003

Mechanisms of Action:¹⁻²

Naproxen competitively inhibits both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, by blocking arachidonate binding; analgesic, antipyretic, and anti-inflammatory pharmacologic effects result from this inhibition. Lansoprazole inhibits basal and stimulated gastric acid secretion irrespective of the stimulus. It belongs to the substituted benzimidazole class of antisecretory agents, which suppress gastric acid secretion by inhibiting the H⁺/K⁺ ATPase enzyme system of gastric parietal cells.

FDA Approved Indications:¹⁻²

This combination product is indicated for reducing the risk of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers in patients with a history of documented gastric ulcer who require the use of an NSAID for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Contraindications:¹⁻²

- Hypersensitivity or allergic reactions to any component of the formulation
- Patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, urticaria, rhinitis, nasal polyps, or allergic-type reactions.



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Pharmacokinetics:¹⁻²

	Naproxen	Lansoprazole
<i>Absorption:</i>	95% bioavailability; peak plasma levels reached in 2-4 hours	80% bioavailability; mean C _{max} occurring ~1.7 hours
<i>Protein Binding:</i>	Greater than 99% albumin-bound	97% bound to plasma proteins
<i>Metabolism:</i>	Hepatic	Hepatic
<i>Elimination:</i>	Urine (95%)	Feces (67%), Urine (33%)
<i>Half-life:</i>	12-17 hours	Less than 2 hours

C_{max} = maximum plasma concentration

Adverse Effects:¹⁻²

Body System	Naproxen (N=960)	Lansoprazole (%) (N=2768)
Body as a Whole		
Back pain	--	<1.0
Hearing disturbances	√	--
Tinnitus	√	--
Visual disturbances	√	--
Cardiovascular		
Dyspnea	√	--
Edema	√	--
Palpitation	√	--
Central Nervous System		
Dizziness	√	<1.0
Drowsiness	√	--
Headache	√	>1.0
Lightheadedness	√	--
Vertigo	√	--
Digestive		
Abdominal pain	√	2.1
Constipation	√	1.0
Diarrhea	√	3.8
Dyspepsia	√	--
Heartburn	√	--
Nausea	√	1.3
Stomatitis	√	--
Vomiting	--	<1.0
Dermatologic		
Ecchymoses	√	--
Pruritis	√	--
Purpura	√	--
Skin eruptions	√	<1.0
Sweating	√	--

√ = reported

Drug Interactions:¹⁻²

Precipitant Drug	Object Drug		Description
Naproxen	ACE inhibitors	↑	NSAIDs may potentiate renal disease states, may diminish anti-hypertensive effect of ACE inhibitors.
Naproxen	Beta blockers	↓	NSAIDs may inhibit antihypertensive effects.
Naproxen, lansoprazole	Warfarin	↑	Monitoring of prothrombin times/INR is advised.
Naproxen	Furosemide	↓	NSAIDs may inhibit natriuretic effect of furosemide.
Naproxen	Methotrexate	↑	May increase methotrexate toxicity
Probenecid	Naproxen	↑	Extends plasma half-life of naproxen
Aspirin	Naproxen	↓	Results in lower naproxen plasma concentrations and peak plasma levels
Lansoprazole	pH-dependent drugs	↑↓	May interfere with absorption of these drugs (e.g., ketoconazole, ampicillin esters, iron salts, digoxin)
Lansoprazole	Theophylline	↓	May increase theophylline clearance by 10%
Sucralfate, antacids	Lansoprazole	↓	Absorption and bioavailability of lansoprazole reduced
Omeprazole, PPI's	Atazanavir	↓	Reduction in atazanavir AUC and Cmin of 76% and 78%, respectively
Antacids/Sucralfate	Naproxen	↓	Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.
Cholestyramine	Naproxen	↓	Concomitant administration of cholestyramine can delay the absorption of naproxen
Naproxen	Methotrexate	↓	Reduce tubular secretion; may enhance toxicity of methotrexate
Naproxen, NSAIDs	SSRIs		Increased risk of GI bleeding

Precaution/Warnings:¹⁻²

- NSAIDs, including naprosyn, can cause serious GI adverse events (with or without warning) including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal.
- Epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper GI bleeding. In two studies, concurrent use of an NSAID or aspirin potentiated the risk of

bleeding. Although these studies focused on upper GI bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated

- Long-term administration of naproxen has resulted in renal papillary necrosis and other renal injury. Administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation.
- Elevation of one or more liver tests, fluid retention and edema have been observed with naproxen therapy. Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients.
- Naproxen-containing products should not be used concomitantly.
- Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.
- Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs have induced the syndrome of asthma, urticaria, or allergic-type reactions.
- Anaphylactoid Reactions: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Naprosyn and/or Prevacid. Naprosyn should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs

Pregnancy/Lactation:¹⁻²

- The naproxen/lansoprazole combination is classified as pregnancy category B.
- Naproxen has been found in the milk of lactating women; it is not known whether lansoprazole is excreted in human breast milk. Use of the combination should be avoided in nursing mothers.

Usual Dosage:¹⁻²

Take the PREVACID 15-mg capsule and one NAPROSYN 500mg tablet in the morning before eating with a glass of water. Take the second NAPROSYN tablet in the evening with a glass of water.

Availability:¹⁻²



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Indiana Medicaid Therapeutics Committee
Prevacid® NapraPAC™ Monograph

Each weekly blister card contains sufficient product for 7 days of treatment, and is packaged as a monthly (28 day) course of therapy. Each daily dose consists of one PREVACID 15-mg capsule and 2 NAPROSYN 500mg tablets.

Clinical Studies:

Title & Author	Study Design	Results
<p>Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs. Results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs. lansoprazole</p> <p>Graham DY, et al.³ (2002)</p>	<p>In a 12-week, randomized, double-blind, active- and placebo-controlled study, 537 patients currently on an NSAID were assigned to receive either misoprostol (200µg QID with or after meals and a bedtime snack), lansoprazole (15 or 30mg QD before breakfast), or placebo.</p> <p><u>Eligibility criteria:</u> Eligible subjects were 18 years or older with a history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or gastrointestinal bleeding, and treatment with stable, full therapeutic doses of an NSAID (with the exception of nabumetone or aspirin [$\geq 1300\text{mg/day}$; low-dose aspirin for cardiovascular protection was permitted]) for at least the previous month.</p> <p>Those patients positive for <i>Helicobacter pylori</i> were excluded, as were those with gastric or duodenal ulcer craters, severe erosions, or erosive reflux esophagitis.</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • Proportion of NSAID patients free of ulcers <p>Efficacy: misoprostol > 15mg lansoprazole \geq 30mg lansoprazole > placebo</p> <ul style="list-style-type: none"> • Patients taking an NSAID in the 15 and 30mg lansoprazole groups remained free from gastric ulcer significantly longer than those who received placebo ($P < 0.001$). There was no difference between lansoprazole groups ($P = 0.62$). • Patients in the misoprostol group remained free of gastric ulcer significantly longer than those who received placebo ($P < 0.001$), 15mg lansoprazole ($P = 0.01$), or 30mg lansoprazole ($P = 0.04$) • Absence of gastric ulcer after 8 or 12 weeks of treatment was different among those receiving placebo, misoprostol, or lansoprazole. By week 12, the percentages of evaluable patients who were free of gastric ulcer were 51%, 93%, 80%, and 82% for the respective treatment groups. • In a subset analysis ($n = 119$), 89% of patients taking 15mg lansoprazole plus naproxen (with or without aspirin) remained free of recurrent gastric ulcers after 12 weeks vs. 83% of patients taking misoprostol or 30mg lansoprazole, and 33% of patients taking placebo plus naproxen (all $P < 0.001$ vs. placebo). <p>Safety: placebo \geq 15mg lansoprazole \approx 30mg lansoprazole > misoprostol</p> <ul style="list-style-type: none"> • More than 90% of patients in the placebo and 15 and 30mg lansoprazole groups were compliant with study medication, compared with 73% of patients in the misoprostol group ($P < 0.001$). • The most commonly reported treatment-related event was diarrhea, which was more common in the misoprostol group (22%) compared with placebo (3%), 15mg lansoprazole (3%), and 30mg lansoprazole (7%) groups (all $P \leq 0.001$ vs. misoprostol). • The misoprostol group also had significantly greater risk of abdominal pain (6%) and nausea (4%) compared with patients in the 15mg lansoprazole group (both 0%) ($P = 0.03$ and $P = 0.01$, respectively).
<p>Celecoxib Plus Aspirin Versus Naproxen and Lansoprazole Plus</p>	<p>In a 12 week, randomized, double blind, study, 1045 subjects were prescribed open-label aspirin and</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • Rate of endoscopically confirmed gastroduodenal ulcers <p>Efficacy: naproxen plus lansoprazole = celecoxib</p>

Title & Author	Study Design	Results
<p>Aspirin: A Randomized, Double-Blind, Endoscopic Trial</p> <p>Goldstein JL, et al.⁴ (2007)</p>	<p>blindly randomized to celecoxib 200 mg QD or naproxen 500 mg BID plus lansoprazole 30 mg QD. Endoscopy was performed at 12 weeks or early termination.</p> <p><u>Eligibility Criteria</u> Subjects 18 years or older with osteoarthritis, without gastroduodenal ulcer or erosive esophagitis at baseline endoscopy, and a cardiovascular indication for prophylaxis low-dose (81 or 325 mg) aspirin</p>	<p><i>plus lansoprazole</i></p> <ul style="list-style-type: none"> • Rate of endoscopically confirmed gastroduodenal ulcers was not different in the celecoxib (9.9%) and naproxen plus lansoprazole (8.9%; treatment difference [95% confidence interval], 1.0% [-2.9% to 4.9%])

Summary:

Prevacid® NapraPAC™ contains the NSAID naproxen and the proton pump inhibitor lansoprazole in one package. Naproxen and other NSAIDs are widely used for the relief of pain and inflammation associated with arthritis and other musculoskeletal disorders. However, the benefit of these drugs is not without the risk of developing serious, life-threatening ulcer complications. With the advent of proton pump inhibitors, more profound acid suppression with these drugs has been reported as being associated with the acceleration of ulcer healing and prevention of ulcer relapse among long-term users of NSAIDs. One clinical study showed that the concomitant use of naproxen and lansoprazole 15mg could better prevent recurrent gastric ulcers compared with naproxen plus misoprostol or placebo. Another clinical study demonstrated that, in patients with osteoarthritis taking low-dose aspirin, the use of celecoxib or naproxen plus lansoprazole resulted in similar rates of gastroduodenal ulceration. Lansoprazole has additional advantages over misoprostol, including once daily dosing and decreased risk of adverse events. Therefore, this combination represents an option in one prescription for arthritis/pain patients who must take NSAIDs to relieve their pain, but who also need to reduce the risk of recurrence of stomach ulcers.

REFERENCES

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4. Goldstein JL, Cryer B, Amer F, Hunt B. Celecoxib Plus Aspirin Versus Naproxen and Lansoprazole Plus Aspirin: A Randomized, Double-Blind, Endoscopic Trial. *Clinical Gastroenterology and Hepatology* 2007;5(10):1167-1174