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Delayed-Release Lansoprazole plus Naproxen

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Contents

Abstract

- A combination package containing delayed-release capsules of the proton pump inhibitor lansoprazole (15mg once daily) and tablets of the NSAID naproxen (375 or 500mg twice daily) has been approved for reducing the risk of NSAID-associated gastric ulcers in NSAID-requiring patients with a documented history of gastric ulcer.
- In a large, 12-week trial in NSAID (including naproxen)-requiring patients with a documented history of gastric ulcer, significantly more recipients of delayed-release lansoprazole 15mg once daily than placebo recipients were free from gastric ulcer ($p < 0.001$). At week 12, the percentages of patients who were free from gastric ulcer were 80% with lansoprazole 15mg and 51% with placebo.
- In a subgroup analysis of recipients of naproxen (89% received 750–1000 mg/day), the percentage of patients free from gastric ulcer after 12 weeks of treatment was significantly higher with delayed-release lansoprazole 15mg than with placebo (89% vs 33%; $p < 0.001$).
- In NSAID (including naproxen)-requiring patients with a documented history of gastric ulcer, the incidence of treatment-related adverse events in recipients of delayed-release lansoprazole 15mg once daily was low (7%), and similar to that in recipients of placebo (10%).

Features and properties of delayed-release lansoprazole capsules plus naproxen tablet combination package (Prevacid® Naprapac™)

Indications		
Risk reduction of NSAID-associated gastric ulcers in patients with a history of documented gastric ulcer who require the use of an NSAID for the treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis		
	Lansoprazole	**Naproxen**
Mechanism of action		
	Proton pump inhibitor	NSAID
Dosage and administration		
Recommended dose	15mg	375 or 500mg
Route of administration	Oral	Oral
Frequency of administration	Once daily	Twice daily
Steady-state pharmacokinetics in healthy volunteers		
Peak plasma concentration (C_{max})	351 ng/mL	79.9–94.8 mg/L (375mg twice daily) and 81.2–110 mg/L (500mg twice daily)
Time to C_{max}	1.5h	1–5h
Plasma half-life	≈1h	12–17h
Adverse events		
Most frequent	Diarrhoea, nausea, headache, abdominal pain	Abdominal pain, nausea, heartburn, constipation, headache, dizziness, drowsiness, mild skin reactions, tinnitus, oedema, dyspnoea

NSAIDs are commonly used for the relief of pain and inflammation associated with arthritis and other musculoskeletal disorders.[1] However, their use is associated with an increased risk of developing gastrointestinal adverse effects, ranging from dyspepsia to gastroduodenal mucosal damage to ulcer complications.[2,3] Acid suppression with proton pump inhibitors offers a means of decreasing the risk of developing NSAID-associated ulcers.[4]

The US FDA has recently approved a combination package (Prevacid® Naprapac™)[1] that contains delayed-release lansoprazole (proton pump inhibitor) capsules and naproxen (NSAID) tablets.[5] This profile focuses on the efficacy of delayed-release lansoprazole for reducing the risk of NSAID-associated gastric ulcer relapse in chronic users of NSAIDs (including naproxen) who have a history of endoscopically documented gastric ulcer. The pharmacological properties and the tolerability of lansoprazole and naproxen are also outlined.

1. Pharmacodynamic Properties

Since the pharmacodynamic properties of both lansoprazole and naproxen are well established,[6-9] only a brief summary of these properties is reported.

Lansoprazole

- Lansoprazole dose dependently inhibits both basal and stimulated gastric acid secretion by inhibition of the H^+/K^+-adenosine triphosphate system, the final step in gastric acid secretion by the gastric parietal cells.[6]
- Lansoprazole 15mg once daily for 5 days significantly increased 24-hour mean gastric pH in healthy volunteers ($p < 0.05$ vs baseline), with a mean 24-hour gastric pH of 4 on day 5. Over a 24-hour period, the mean percentage of time that the gastric pH was >3 or >4 on day 5 was 59% and 49% (both $p < 0.05$ vs baseline).[5,10]
- At steady state, gastric pH increased 1–2 hours after administration of a dose of lansoprazole 15mg.[5]
- Multiple-dose lansoprazole 15mg once daily was associated with a reversible increase in fasting serum gastrin levels (mean 57%; $p < 0.05$ vs baseline), but none of the healthy volunteers had an increase more than twice the upper limit of normal.[10]
- Multiple-dose lansoprazole 15mg once daily reduced meal-stimulated[11] and pentagastrin-stimulated[12] gastric acid secretion in healthy volunteers ($p < 0.05$ vs placebo).

Naproxen

- Naproxen possesses analgesic, antipyretic and anti-inflammatory properties that are thought to be related to its inhibition of cyclo-oxygenase and consequent decrease in prostaglandin levels in tissues and fluids such as the gastric mucosa, synovial fluid, urine and blood.[8,9]
- In common with other NSAIDs, naproxen has been associated with gastrointestinal microbleeding and endoscopically proven gastrointestinal lesions (see section 4).[2,8]

2. Pharmacokinetic Properties

Since the pharmacokinetic properties of oral lansoprazole and oral naproxen are well established,[6-8] only a brief summary of these properties is reported.

Because of the acid-labile nature of lansoprazole, the delayed-release lansoprazole capsules contain an enteric-coated granule formulation of lansoprazole that delays absorption of the drug until the granules have left the stomach.[5]

Lansoprazole

- Lansoprazole is rapidly and almost completely absorbed after oral administration (absolute bioavailability >80%).[6] The mean steady-state peak plasma concentration (C_{max}) of lansoprazole 15mg was 351 ng/mL, and occurred after 1.5 hours; [10] the mean steady-sate area under the plasma concentration-time curve (AUC) was 723 ng • h/mL.[10]
- Lansoprazole displays linear kinetics over a single-dose range of 15–60mg.[6] The drug does not

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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accumulate, and multiple dosing does not alter its pharmacokinetics.[5]

- Lansoprazole is highly bound to plasma proteins (≈97%).[6]
- The mean C_{max} and AUC of lansoprazole are reduced by about 50–70%, if the drug is administered 30 minutes after food,[5,6] but there is no effect on these parameters when lansoprazole is administered before food.
- The mean plasma elimination half-life ($t_{1/2}\beta$) of lansoprazole 15mg at steady state was approximately 1 hour.[10] After a single oral dose of [^{14}C]lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the faeces.[6]
- Lansoprazole is extensively metabolised in the liver by cytochrome P450 (CYP) enzymes to two metabolites with little or no antisecretory activity (the hydroxylated sulfinyl and sulfone derivatives). However, lansoprazole is thought to be converted to two active metabolites within the parietal cells; these active metabolites are not present within the systemic circulation. This may explain why the drug has anti-secretory activity lasting more than 24 hours, yet has a short $t_{1/2}\beta$ of ≈1 hour.[5,6]
- The $t_{1/2}\beta$ and AUC of lansoprazole were decreased in patients with renal impairment and increased in patients with hepatic impairment.[6]

Naproxen

- Oral naproxen is rapidly and completely absorbed (mean absolute bioavailability 95%) from the gastrointestinal tract.[5,7] Mean steady-state C_{max} values in healthy volunteers for naproxen 375mg twice daily were 79.9–94.8 mg/L and for 500mg twice daily were 81.2–110 mg/L; these levels were attained 1–5 hours after administration.[7] Steady-state plasma naproxen concentrations were reached after 4–5 days.[5]
- At doses of naproxen >500 mg/day, there is a less than dose-proportional increase in plasma levels as a result of the increase in the total renal clearance of naproxen (a consequence of the saturation of plasma protein binding sites). However, the concentration of unbound naproxen continues to increase in proportion to the naproxen dose.[7]
- Naproxen is highly protein bound (>99%); the volume of distribution is 0.1–0.2 L/kg.[7]
- Naproxen is extensively metabolized by CYP enzymes to 6-*O*-desmethylnaproxen.[7]
- Approximately 95% of a dose of naproxen is excreted in the urine, mainly as unchanged naproxen (<1%), 6-*O*-desmethylnaproxen (<1%) or their conjugates (66–92%).[5] The $t_{1/2}\beta$ of naproxen is about 12–17 hours.[5]

3. Therapeutic Efficacy

A double-blind, multicentre study investigated the efficacy of delayed-release lansoprazole for preventing the relapse of NSAID-associated gastric ulcer in patients without *Helicobacter pylori* infection who were long-term users of NSAIDs (including naproxen) and had a history of endoscopically documented gastric ulcer.[13] Patients (n = 537) were randomised to receive 12 weeks' treatment with delayed-release lansoprazole 15 or 30mg once daily, misoprostol 200μg four times daily or placebo. The misoprostol treatment arm was not blinded. Ulcer status was determined by endoscopy with biopsy at 4, 8 and 12 weeks. NSAID treatment, including ibuprofen (40% of patients), naproxen (35%), diclofenac (32%), piroxicam (17%), other NSAIDs (34%) or aspirin (acetylsalicylic acid) or aspirin combinations (22%), continued throughout the trial.

A retrospective subset analysis of 119 patients who received naproxen (figure 1 for dosages) in this double-blind trial was reported in an abstract[14] and in the prescribing information for the combination package of lansoprazole plus naproxen.[5] Fifteen percent of these patients also received low-dose aspirin.

- In the large multicentre trial,[5,13] significantly more recipients of lansoprazole 15mg once daily than placebo recipients were free from gastric ulcer ($p < 0.001$). A similar number of recipients of once-daily lansoprazole 15 or 30mg were free from gastric ulcer. Significantly more misoprostol recipients were ulcer-free than lansoprazole recipients ($p < 0.05$), but after adjustment for acute baseline

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gastric ulcer size (measured during an screening endoscopy prior to study entry), statistically significant differences between the active treatment groups disappeared.

- At week 12, the percentages of patients who were free from gastric ulcer were 51% with placebo (95% CI 41.1%, 61.3%), 80% with lansoprazole 15mg (95% CI 72.5%, 87.3%), 82% with lansoprazole 30mg (95% CI 75.0%, 89.6%) and 93% with misoprostol (95% CI 87.2%, 97.9%).[13]
- In the subgroup analysis of naproxen recipients,[5,14] the percentage of patients free from gastric ulcer after 12 weeks of treatment was significantly higher with lansoprazole 15mg once daily than with placebo ($p < 0.001$) [see figure 1]; there was no significant difference between the active treatment groups.[14]

4. Tolerability

The tolerability of lansoprazole and naproxen has been extensively reviewed in *Drugs*.[6,8] The brief outline of the tolerability of these agents presented here focuses on the tolerability data presented in the trial outlined in section 3.[13,14]

- Lansoprazole is well tolerated and had a similar tolerability profile to that of placebo in short- and long-term clinical trials.[6,15] The most common adverse events are diarrhoea, nausea, headache and abdominal pain. These events occurred in ≤5% of patients in short-term trials (≤12 weeks), but occurred more frequently with long-term administration (≤10%). The adverse event profile of lansoprazole is similar to that of comparative agents (omeprazole, ranitidine).[6]
- Long-term (up to 4 years) treatment with lansoprazole has not been associated with any gastric endocrine or non-endocrine cell neoplastic or dysplastic changes.[15]
- Naproxen is generally well tolerated.[8] In common with other NSAIDs, the most common treatment-related adverse events (occurring in 3–9% of recipients) involve the gastrointestinal tract (abdominal pain, nausea, heartburn, constipation) or the central nervous system (headache, dizziness, drowsiness). Mild skin reactions, tinnitus, oedema and dyspnoea have also been commonly reported. Gastrointestinal bleeding and ulceration occur in <1% of patients.[5]

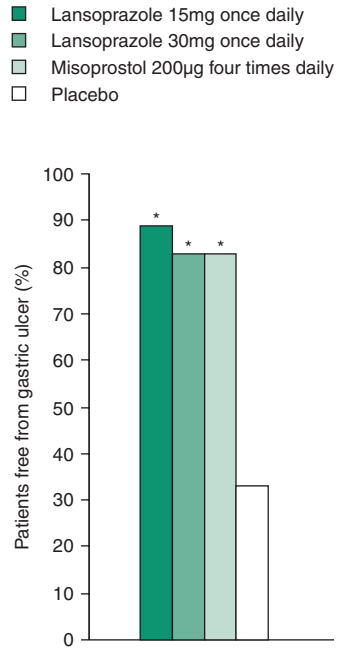

Fig. 1. Percentage of naproxen-treated patients free from gastric ulcer after treatment with delayed-release lansoprazole, misoprostol or placebo. Data are presented from a retrospective subset analysis[5,14] of naproxen-treated patients enrolled in a randomised, double-blind, multicentre trial[13] in NSAID-requiring patients with evidence of gastric ulcer. Patients received 12 weeks' treatment with delayed-release lansoprazole 15mg once daily (n = 37) or 30mg once daily (n = 24), misoprostol 200µg four times daily (n = 28) or placebo (n = 30). The misoprostol treatment arm was not blinded. In lansoprazole recipients, five also received naproxen <750 mg/day, 54 received naproxen 750–1000 mg/day and two received >1000 mg/day. * $p < 0.001$ vs placebo.

- As with other NSAIDs and drugs that have been extensively used in clinical practice, rare serious adverse events have occurred with naproxen; these include gastrointestinal bleeding and ulceration.[8]
- In the trial outlined in section 3,[13] the incidence of adverse events with delayed-release lansoprazole 15mg (7%) was similar to that with placebo (10%), and significantly less than that with lansoprazole 30mg (16%; $p = 0.04$) or misoprostol (31%; $p < 0.001$), in NSAID-treated patients. Moreover, the incidence of diarrhoea (3% vs 22%; $p \leq 0.001$), abdominal pain (0% vs 6%; $p = 0.003$) and nausea

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(0% vs 4%; p = 0.01) was significantly lower with lansoprazole 15mg than with misoprostol.[13]

- In the subgroup analysis of naproxen recipients in the trial outlined in section 3, the incidence of diarrhoea was 3%, 8%, 18% and 3% in recipients of lansoprazole 15mg, lansoprazole 30mg, misoprostol, or placebo, respectively; however, there were no statistically significant between-group differences.[14]

5. Dosage and Administration

The combination package contains delayed-release lansoprazole 15mg once daily for the risk reduction of NSAID-associated gastric ulcers and naproxen 375 or 500mg twice daily for NSAID-requiring patients with a documented history of gastric ulcer.[5]

6. Lansoprazole plus Naproxen: Current Status

The combination package of lansoprazole delayed-release capsules (15mg once daily) and naproxen tablets (375 or 500mg twice daily) has recently been approved by the US FDA for risk reduction of NSAID-associated gastric ulcers in patients with a history of documented gastric ulcer who require the use of an NSAID for the treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. According to a retrospective analysis of a large clinical trial in of naproxen-treated, *H. pylori*-negative patients with a documented history of gastric ulcer, once-daily administration of delayed-release lansoprazole 15mg was effective in preventing gastric ulcers and was generally well tolerated.

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