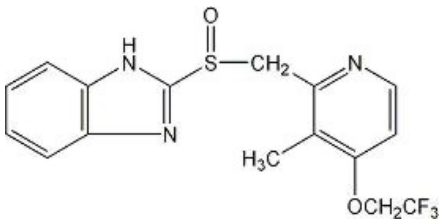
PREVACID® (lansoprazole) Delayed-Release Capsules

PREVACID® (lansoprazole) For Delayed-Release Oral Suspension

PREVACID® SoluTab™ (lansoprazole) Delayed-Release Orally Disintegrating Tablets

DESCRIPTION

The active ingredient in PREVACID® Delayed-Release Capsules, PREVACID® for Delayed-Release Oral Suspension and PREVACID® SoluTab™ Delayed-Release Orally Disintegrating Tablets is lansoprazole, a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. PREVACID has the following structure:



Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

PREVACID is supplied in delayed-release capsules, in delayed-release orally disintegrating tablets for oral administration and in a packet for delayed-release oral suspension.

The delayed-release capsules are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of 15 mg or 30 mg of lansoprazole (active ingredient) and the following inactive ingredients: hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3PREVACID 15-mg capsules only., and FD&C Red No. 40 (inactive ingredients).

PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per tablet. Each delayed-release orally disintegrating tablet contains enteric-coated microgranules consisting of 15 mg or 30 mg of lansoprazole (active ingredient) and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium carbonate, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid, polyacrylate, polyethylene glycol, glyceryl monostearate, polysorbate 80, triethyl citrate, ferric oxide, citric acid, crospovidone, aspartamePhenylketonurics: Contains Phenylalanine 2.5 mg per 15 mg Tablet and 5.1 mg per 30 mg Tablet., artificial strawberry flavor and magnesium stearate.

PREVACID for Delayed-Release Oral Suspension are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per packet. Each packet of delayed-release oral suspension contains enteric-coated granules consisting of 15 or 30 mg of lansoprazole (active ingredient) and the following inactive ingredients (inactive granules): confectioner's sugar, mannitol, docusate sodium, ferric oxide, colloidal silicon dioxide, xanthan gum, crospovidone, citric acid, sodium citrate, magnesium stearate, and artificial strawberry flavor. The lansoprazole granules and inactive granules, present in unit dose packets, are constituted with water to form a suspension and consumed orally.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

PREVACID Delayed-Release Capsules, PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets and PREVACID for Delayed-Release Oral Suspension contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. After a single-dose administration of 15 mg to 60 mg of oral lansoprazole, the peak

Special Populations

Pharmacodynamics

Microbiology

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of Helicobacter pylori in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

CLINICAL STUDIES

Duodenal Ulcer

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, and 60 mg of PREVACID once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after two and four weeks was significantly higher with all doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the two higher doses compared with PREVACID 15 mg. Based on this study and the second study described below, the recommended dose of PREVACID in duodenal ulcer is 15 mg per day (Table 4).

Table 4: Duodenal Ulcer Healing Rates

	PREVACID 15 mg daily	30 mg daily	60 mg daily	Placebo
Week	(N=68)	(N=74)	(N=70)	(N=72)
2	42.4% (p≤0.001) versus placebo.	35.6%	39.1%	11.3%
4	89.4%	91.7%	89.9%	46.1%

PREVACID 15 mg was significantly more effective than placebo in relieving day and nighttime abdominal pain and in decreasing the amount of antacid taken per day.

In a second U.S. multicenter study, also double-blind, placebo-controlled, dose-comparison (15 and 30 mg of PREVACID once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after four weeks was significantly higher with both doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the higher dose of PREVACID. Although the 15 mg dose of PREVACID was superior to ranitidine at 4 weeks, the lack of significant difference at 2 weeks and the absence of a difference between 30 mg of PREVACID and ranitidine leaves the comparative effectiveness of the two agents undetermined (Table 5).

Table 5: Duodenal Ulcer Healing Rates

	PREVACID 15 mg daily	30 mg daily	Ranitidine 300 mg h.s.	Placebo
Week	(N=80)	(N=77)	(N=82)	(N=41)
2	35.0%	44.2%	30.5%	34.2%
4	92.3% (p≤0.05) versus placebo and ranitidine.	80.3% (p≤0.05) versus placebo.	70.5%	47.5%

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Randomized, double-blind clinical studies performed in the U.S. in patients with H. pylori and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of PREVACID in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy or in combination with amoxicillin capsules as dual 14-day therapy for the eradication of H. pylori. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy:	PREVACID 30 mg b.i.d./ amoxicillin 1 gm b.i.d./ clarithromycin 500 mg b.i.d.
Dual therapy:	PREVACID 30 mg t.i.d./ amoxicillin 1 gm t.i.d.

All treatments were for 14 days. H. pylori eradication was defined as two negative tests (culture and histology) at 4-6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with H. pylori and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of PREVACID triple therapy for 10 and 14 days. This study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating H. pylori (Tables 6 and 7).

Table 6

H. pylori Eradication Rates – Triple Therapy (PREVACID/amoxicillin/clarithromycin) Percent of Patients Cured [95% Confidence Interval] (Number of patients)

Triple Therapy Evaluable Analysis	Triple Therapy Intent-to-Treat Analysis
Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and H. pylori infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients	Patients were included in the analysis if they had documented H. pylori infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of

Study	Duration	they were included in the evaluable analysis as failures of therapy.	
M93-131	14 days	92(p<0.05) versus PREVACID/amoxicillin and PREVACID/clarithromycin dual therapy [80.0-97.7] (N=48)	86 [73.3-93.5] (N=55)
M95-392	14 days	86(p<0.05) versus clarithromycin/amoxicillin dual therapy [75.7-93.6] (N=66)	83 [72.0-90.8] (N=70)
M95-399The 95% confidence interval for the difference in eradication rates, 10-day minus 14-day is (-10.5, 8.1) in the evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.	14 days	85 [77.0-91.0] (N=113)	82 [73.9-88.1] (N=126)
	10 days	84 [76.0-89.8] (N=123)	81 [73.9-87.6] (N=135)

Table 7

H. pylori Eradication Rates – 14-Day Dual Therapy (PREVACID/amoxicillin) Percent of Patients Cured [95% Confidence Interval] (Number of patients)

Study	Dual Therapy Evaluable AnalysisBased on evaluable patients with confirmed duodenal ulcer (active or within one year) and H. pylori infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.	Dual Therapy Intent-to-Treat AnalysisPatients were included in the analysis if they had documented H. pylori infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.
M93-131	77(p<0.05) versus PREVACID alone. [62.5-87.2] (N=51)	70 [56.8-81.2] (N=60)
M93-125	66 (p<0.05) versus PREVACID alone or amoxicillin alone. [51.9-77.5] (N=58)	61 [48.5-72.9] (N=67)

Long-Term Maintenance Treatment of Duodenal Ulcers

PREVACID has been shown to prevent the recurrence of duodenal ulcers. Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed duodenal ulcers. Patients remained healed significantly longer and the number of recurrences of duodenal ulcers was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period (Table 8).

Table 8: Endoscopic Remission Rates

			Percent in Endoscopic Remission		
Trial	**Drug**	**No. of Pts.**	**0-3 mo.**	**0-6 mo.**	**0-12 mo.**
#1	PREVACID 15 mg daily	86	90%(p≤0.001) versus placebo.	87%	84%
	Placebo	83	49%	41%	39%
#2	PREVACID 30 mg daily	18	94%	94%	85%
	PREVACID 15 mg daily	15	87%	79%	70%*
	Placebo	15	33%	0%	0%

%=Life Table Estimate

In trial #2, no significant difference was noted between PREVACID 15 mg and 30 mg in maintaining remission.

Gastric Ulcer

In a U.S. multicenter, double-blind, placebo-controlled study of 253 patients with endoscopically documented gastric ulcer, the percentage of patients healed at four and eight weeks was significantly higher with PREVACID 15 mg and 30 mg once a day than with placebo (Table 9).

Table 9: Gastric Ulcer Healing Rates

	PREVACID			Placebo
	15 mg daily	30 mg daily	60 mg daily	
Week	**(N=65)**	**(N=63)**	**(N=61)**	**(N=64)**
4	64.6%(p≤0.05) versus placebo.	58.1%	53.3%	37.5%
8	92.2%	96.8%	93.2%	76.7%

Patients treated with any PREVACID dose reported significantly less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets used per day than the placebo group.

Independent substantiation of the effectiveness of PREVACID 30 mg was provided by a meta-analysis of published and unpublished data.

Healing of NSAID-Associated Gastric Ulcer

In two U.S. and Canadian multicenter, double-blind, active-controlled studies in patients with endoscopically confirmed

female patients and 33% male patients. Race was distributed as follows: 87% Caucasian, 8% Black, 5% other. There was no statistically significant difference between PREVACID 30 mg daily and the active control on symptom relief (i.e., abdominal pain) (Table 10).

Table 10: NSAID-Associated Gastric Ulcer Healing RatesActual observed ulcer(s) healed at time points ± 2 days

	Study #1	
	PREVACID 30 mg daily	Active Control Dose for healing of gastric ulcer
Week 4	60% (53/88) (p≤0.05) versus the active control	28% (23/83)
Week 8	79% (62/79)	55% (41/74)
	Study #2	
	PREVACID 30 mg daily	Active Control
Week 4	53% (40/75)	38% (31/82)
Week 8	77% (47/61)	50% (33/66)

Risk Reduction of NSAID-Associated Gastric Ulcer

In one large U.S., multicenter, double-blind, placebo- and misoprostol-controlled (misoprostol blinded only to the endoscopist) study in patients who required chronic use of an NSAID and who had a history of an endoscopically documented gastric ulcer, the proportion of patients remaining free from gastric ulcer at 4, 8, and 12 weeks was significantly higher with 15 or 30 mg of PREVACID than placebo. A total of 537 patients were enrolled in the study, and 535 patients were treated. Patients ranged in age from 23 to 89 years (median age 60 years), with 65% female patients and 35% male patients. Race was distributed as follows: 90% Caucasian, 6% Black, 4% other. The 30 mg dose of PREVACID demonstrated no additional benefit in risk reduction of the NSAID-associated gastric ulcer than the 15 mg dose (Table 11).

Table 11: Proportion of Patients Remaining Free of Gastric Ulcers% = Life Table Estimate
(p<0.001) PREVACID 15 mg daily versus placebo; PREVACID 30 mg daily versus placebo; and misoprostol 200 µg q.i.d. versus placebo.
(p<0.05) Misoprostol 200 µg q.i.d. versus PREVACID 15 mg daily; and misoprostol 200 µg q.i.d. versus PREVACID 30 mg daily

Week	PREVACID 15 mg daily (N=121)	PREVACID 30 mg daily (N=116)	Misoprostol 200 µg q.i.d. (N=106)	Placebo (N=112)
4	90%	92%	96%	66%
8	86%	88%	95%	60%
12	80%	82%	93%	51%

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration of lansoprazole 15 mg once daily up to 8 weeks than with placebo. No significant additional benefit from lansoprazole 30 mg once daily was observed.

The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period are presented in Table 12 and in Figures 1 and 2:

Table 12: Frequency of Heartburn

Variable	Placebo (n=43)	PREVACID 15 mg (n=80)	PREVACID 30 mg (n=86)
	Median		
% of Days without Heartburn			
Week 1	0%	71%(p<0.01) versus placebo.	46%
Week 4	11%	81%	76%
Week 8	13%	84%	82%
% of Nights without Heartburn			
Week 1	17%	86%	57%
Week 4	25%	89%	73%
Week 8	36%	92%	80%

Figure 1

Figure 2

In two U.S., multicenter double-blind, ranitidine-controlled studies of 925 total patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, lansoprazole 15 mg was superior to ranitidine 150 mg (b.i.d.) in decreasing the frequency and severity of day and night heartburn associated with GERD for the 8-week treatment period. No significant additional benefit from lansoprazole 30 mg once daily was observed.

Long-Term Maintenance Treatment of Erosive Esophagitis

Two independent, double-blind, multicenter, controlled trials were conducted in patients with endoscopically confirmed healed esophagitis. Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with PREVACID than in patients treated with placebo over a 12-month period (Table 16).

Table 16: Endoscopic Remission Rates

	Percent in Endoscopic Remission

#1	PREVACID 15 mg daily	59	versus placebo.	81%	79%
	PREVACID 30 mg daily	56	93%	93%	90%
	Placebo	55	31%	27%	24%
#2	PREVACID 15 mg daily	50	74%	72%	67%
	PREVACID 30 mg daily	49	75%	72%	55%
	Placebo	47	16%	13%	13%

%=Life Table Estimate

Regardless of initial grade of erosive esophagitis, PREVACID 15 mg and 30 mg were similar in maintaining remission.

In a U.S., randomized, double-blind, study, PREVACID 15 mg daily (n = 100) was compared with ranitidine 150 mg b.i.d. (n = 106), at the recommended dosage, in patients with endoscopically-proven healed erosive esophagitis over a 12-month period. Treatment with PREVACID resulted in patients remaining healed (Grade 0 lesions) of erosive esophagitis for significantly longer periods of time than those treated with ranitidine ($p<0.001$). In addition, PREVACID was significantly more effective than ranitidine in providing complete relief of both daytime and nighttime heartburn. Patients treated with PREVACID remained asymptomatic for a significantly longer period of time than patients treated with ranitidine.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PREVACID significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia and pain. Doses ranging from 15 mg every other day to 180 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see **DOSAGE AND ADMINISTRATION**). PREVACID was well tolerated at these high dose levels for prolonged periods (greater than four years in some patients). In most ZE patients, serum gastrin levels were not modified by PREVACID. However, in some patients, serum gastrin increased to levels greater than those present prior to initiation of lansoprazole therapy.

INDICATIONS AND USAGE

PREVACID Delayed-Release Capsules, PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets and PREVACID For Delayed-Release Oral Suspension are indicated for:

Short-Term Treatment of Active Duodenal Ulcer

PREVACID is indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Maintenance of Healed Duodenal Ulcers

PREVACID is indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months.

Short-Term Treatment of Active Benign Gastric Ulcer

PREVACID is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer.

Healing of NSAID-Associated Gastric Ulcer

PREVACID is indicated for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks.

Risk Reduction of NSAID-Associated Gastric Ulcer

PREVACID is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks.

Gastroesophageal Reflux Disease (GERD)

Maintenance of Healing of Erosive Esophagitis

PREVACID is indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

PREVACID is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

PREVACID is contraindicated in patients with known severe hypersensitivity to any component of the formulation of PREVACID.

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin.

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, and any of the macrolide antibiotics.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, ergotamine or dihydroergotamine. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

For information about contraindications of other drugs that may be used in combination with amoxicillin or clarithromycin, refer to the CONTRAINDICATIONS section of their package inserts.

Please refer to full prescribing information for amoxicillin and clarithromycin before prescribing.

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