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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PREVACID safely and effectively. See full prescribing information for:

PREVACID (lansoprazole) Delayed-Release Capsules
PREVACID (lansoprazole) For Delayed-Release Oral Suspension
PREVACID SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablets

For oral administration
Initial U.S. Approval: 1995

----------RECENT MAJOR CHANGES----------

Contraindications (4)	April 2008
Warnings and Precautions (5)	April 2008

----------INDICATIONS AND USAGE----------

PREVACID is a proton pump inhibitor (PPI). Refer to DOSAGE and ADMINISTRATION table (below) for indications and usage.

----------DOSAGE AND ADMINISTRATION----------

Indication	Dose	Frequency
Duodenal Ulcers (1.1, 1.3)		
Short-Term Treatment	15 mg	Once daily for 4 wks
Maintenance of Healed	15 mg	Once daily
***H. pylori* Eradication to Reduce Recurrence of Duodenal Ulcer** (1.2)		
Triple Therapy: PREVACID Amoxicillin Clarithromycin	30 mg 1 gram 500 mg	Twice daily for 10 or 14 days
Dual Therapy: PREVACID Amoxicillin	30 mg 1 gram	Three times daily for 14 days
Benign Gastric Ulcer Short-Term Treatment (1.4)	30 mg	Once daily up to 8 wks
NSAID-associated Gastric Ulcer (1.6)		
Healing Risk Reduction	30 mg 15 mg	Once daily for 8 wks Once daily up to 12 wks
GERD (1.7)		
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily up to 8 wks
Short-Term Treatment of EE	30 mg	Once daily up to 8 wks
Pediatric (8.4)		
(1 to 11 years of age) Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of EE		
≤ 30 kg	15 mg	Once daily up to 12 wks
> 30 kg	30 mg	Once daily up to 12 wks
(12 to 17 years of age) Short-Term Treatment of Symptomatic GERD		
Nonerosive GERD	15 mg	Once daily up to 8 wks
EE	30 mg	Once daily up to 8 wks
Maintenance of Healing of EE (1.8)	15 mg	Once daily
Pathological Hypersecretory Conditions (i.e., ZES) (1.9)	60 mg	Once daily

----------DOSAGE FORMS AND STRENGTHS----------

Capsules, Oral Suspensions and Tablets: 15 mg and 30 mg. (3)

----------CONTRAINDICATIONS----------

Contraindicated in patients with known severe hypersensitivity to any component of the PREVACID formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

Symptomatic response with PREVACID does not preclude the presence of gastric malignancy. (5)

----------ADVERSE REACTIONS----------

Most commonly reported adverse reactions (≥1%): diarrhea, abdominal pain, nausea and constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact TAP Pharmaceutical Products Inc. at 1.800.622.2011 or FDA at 1.800.FDA.1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Do not co-administer with atazanavir. (7)
- May interfere with the absorption of drugs where gastric pH is important for bioavailability (7)
- Concomitant warfarin use may require monitoring for increases in INR and prothrombin time. (7)
- Titration of theophylline dosage may be required when concomitant PREVACID use is started or stopped. (7)

----------USE IN SPECIFIC POPULATIONS----------

Consider dose adjustment in patients with severe liver impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: October 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

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1 INDICATIONS AND USAGE

1.1 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. ***[See Clinical Studies (14)]***

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

Triple Therapy: PREVACID/amoxicillin /clarithromycin
PREVACID in combination with amoxicillin plus clarithromycin as triple therapy is indicated for the treatment of patients with ***H. pylori*** infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate ***H. pylori.*** Eradication of ***H. pylori*** has been shown to reduce the risk of duodenal ulcer recurrence. ***[See Clinical Studies (14)]***

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

Dual Therapy: PREVACID/amoxicillin
PREVACID in combination with amoxicillin as dual therapy is indicated for the treatment of patients with ***H. pylori*** infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected** (see the clarithromycin package insert, MICROBIOLOGY section). Eradication of ***H. pylori*** has been shown to reduce the risk of duodenal ulcer recurrence. ***[See Clinical Studies (14)]***

Please refer to the full prescribing information for amoxicillin.

1.3 Maintenance of Healed Duodenal Ulcers

PREVACID is indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months. ***[See Clinical Studies (14)]***

1.4 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. ***[See Clinical Studies (14)]***

1.5 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. ***[See Clinical Studies (14)]***

1.6 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. ***[See Clinical Studies (14)]***

1.7 Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD
PREVACID is indicated for the treatment of heartburn and other symptoms associated with GERD. ***[See Clinical Studies (14)]***

Short-Term Treatment of Erosive Esophagitis

PREVACID is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis.
For patients who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis an additional 8-week course of PREVACID may be considered. ***[See Clinical Studies (14)]***

1.8 Maintenance of Healing of Erosive Esophagitis (EE)

PREVACID is indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months. ***[See Clinical Studies (14)]***

1.9 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

PREVACID is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. ***[See Clinical Studies (14)]***

2 DOSAGE AND ADMINISTRATION

PREVACID is available as a capsule, orally disintegrating tablet and oral suspension, and is available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration for each of these dosage forms is presented below. PREVACID should be taken before eating. PREVACID products SHOULD NOT BE CRUSHED OR CHEWED. In the clinical trials, antacids were used concomitantly with PREVACID.

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2.1 Recommended Dose

Indication	Recommended Dose	Frequency
Duodenal Ulcers		
Short-Term Treatment	15 mg	Once daily for 4 weeks
Maintenance of Healed	15 mg	Once daily
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence†		
Triple Therapy:		
PREVACID	30 mg	Twice daily (q12h) for 10 or 14 days
Amoxicillin	1 gram	Twice daily (q12h) for 10 or 14 days
Clarithromycin	500 mg	Twice daily (q12h) for 10 or 14 days
Dual Therapy:		
PREVACID	30 mg	Three times daily (q8h) for 14 days
Amoxicillin	1 gram	Three times daily (q8h) for 14 days
Benign Gastric Ulcer		
Short-Term Treatment	30 mg	Once daily for up to 8 weeks
NSAID-associated Gastric Ulcer		
Healing	30 mg	Once daily for 8 weeks*
Risk Reduction	15 mg	Once daily for up to 12 weeks*
Gastroesophageal Reflux Disease (GERD)		
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily for up to 8 weeks
Short -Term Treatment of Erosive Esophagitis	30 mg	Once daily for up to 8 weeks**
Pediatric		
(1 to 11 years of age) Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of Erosive Esophagitis		
≤ 30 kg	15 mg	Once daily for up to 12 weeks+
> 30 kg	30 mg	Once daily for up to 12 weeks+
(12 to 17 years of age) Short-Term Treatment of Symptomatic GERD		
Nonerosive GERD	15 mg	Once daily for up to 8 weeks
Erosive Esophagitis	30 mg	Once daily for up to 8 weeks
Maintenance of Healing of Erosive Esophagitis	15 mg	Once daily
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	60 mg	Once daily***

† Please refer to amoxicillin and clarithromycin full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally-impaired patients.
* Controlled studies did not extend beyond indicated duration.
** For patients who do not heal with PREVACID for 8 weeks (5–10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis, an additional 8 week course of PREVACID may be considered.
***Varies with individual patient. Recommended adult starting dose is 60 mg once daily. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg twice daily have been administered. Daily dose of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison Syndrome have been treated continuously with PREVACID for more than 4 years.
+ The PREVACID dose was increased (up to 30 mg twice daily) in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic. For pediatric patients unable to swallow an intact capsule please see Administration Options.

2.2 Special Populations

Renal impairment patients and geriatric patients do not require dosage adjustment. However, consider dose adjustment in patients with severe liver impairment. ***[See Use in Specific Populations (8.5, 8.6 and 8.7]***

2.3 Important Administration Information

Administration Options
PREVACID Delayed-Release Capsules - Oral Administration

- PREVACID Delayed-Release Capsules should be swallowed whole.
- Alternatively, for patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened and administered as follows:
  - Open capsule.
  - Sprinkle intact granules on one tablespoon of either applesauce, ENSURE® pudding, cottage cheese, yogurt or strained pears.
  - Swallow immediately.

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- PREVACID Delayed-Release Capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:
  - Open capsule.
  - Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 mL – approximately 2 ounces).
  - Mix briefly.
  - Swallow immediately.
  - To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

PREVACID Capsules - Nasogastric Tube Administration

- For patients who have a nasogastric tube in place, PREVACID Delayed-Release Capsules can be administered as follows:
  - Open capsule.
  - Mix intact granules into 40 mL of apple juice. DO NOT USE OTHER LIQUIDS.
  - Inject through the nasogastric tube into the stomach.
  - Flush with additional apple juice to clear the tube.

PREVACID SoluTab™ Delayed-Release Orally Disintegrating Tablets

- PREVACID SoluTab should not be chewed.
  - Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed.
  - The tablet typically disintegrates in less than 1 minute.
  - Alternatively, for children or other patients who have difficulty swallowing tablets, PREVACID SoluTab can be delivered in two different ways.

    PREVACID SoluTab – Oral Syringe

    For administration via oral syringe, PREVACID SoluTab can be administered as follows:
    - Place a 15 mg tablet in oral syringe and draw up approximately 4 mL of water, or place a 30 mg tablet in oral syringe and draw up approximately 10 mL of water.
    - Shake gently to allow for a quick dispersal.
    - After the tablet has dispersed, administer the contents within 15 minutes.
    - Refill the syringe with approximately 2 mL (5 mL for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

    PREVACID SoluTab – Nasogastric Tube Administration (≥ 8 French)

    For administration via a nasogastric tube, PREVACID SoluTab can be administered as follows:
    - Place a 15 mg tablet in a syringe and draw up 4 mL of water, or place a 30 mg tablet in a syringe and draw up 10 mL of water.
    - Shake gently to allow for a quick dispersal.
    - After the tablet has dispersed, inject through the nasogastric tube into the stomach within 15 minutes.
    - Refill the syringe with approximately 5 mL of water, shake gently, and flush the nasogastric tube.

PREVACID for Delayed-Release Oral Suspension

PREVACID for Delayed-Release Oral Suspension should be administered as follows:

- Open packet.
- To prepare a dose, empty the packet contents into a container containing 2 tablespoons of **WATER**. DO NOT USE OTHER LIQUIDS OR FOODS.
- Stir well, and drink immediately.
- If any material remains after drinking, add more water, stir, and drink immediately.
- **This product should not be given through enteral administration tubes.**

3 DOSAGE FORMS AND STRENGTHS

- 15 mg capsules are opaque, hard gelatin, colored pink and green with the TAP logo and “PREVACID 15” imprinted on the capsule.
- 30 mg capsules are opaque, hard gelatin, colored pink and black with the TAP logo and “PREVACID 30” imprinted on the capsule.
- 15 and 30 mg oral suspension are white to pale brownish lansoprazole granules and inactive pink granules.
- 15 mg tablets are white to yellowish white, uncoated, colored orange to dark brown speckles with “15” debossed on one side of the tablet.
- 30 mg tablets are white to yellowish white, uncoated, colored orange to dark brown speckles with “30” debossed on one side of the tablet.

4 CONTRAINDICATIONS

PREVACID is contraindicated in patients with known severe hypersensitivity to any component of the formulation of PREVACID.
For information on contraindications for amoxicillin or clarithromycin, refer to their full prescribing information, CONTRAINDICATIONS sections.

5 WARNINGS AND PRECAUTIONS

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.
For information on warnings and precautions for amoxicillin or clarithromycin, refer to their full prescribing information, WARNINGS and PRECAUTIONS sections.

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6 ADVERSE REACTIONS

6.1 Clinical

Worldwide, over 10,000 patients have been treated with PREVACID in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are similar. In general, PREVACID treatment has been well-tolerated in both short-term and long-term trials.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reactions were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of PREVACID-treated patients and occurred at a greater rate in PREVACID-treated patients than placebo-treated patients in Table 1.

Table 1: Incidence of Possibly or Probably Treatment-Related Adverse Reactions in Short-Term, Placebo-Controlled PREVACID Studies

Body System/Adverse Event	PREVACID (N= 2768) %	Placebo (N= 1023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received 15 mg and 30 mg of PREVACID, but higher in the patients who received 60 mg of PREVACID (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of PREVACID for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with PREVACID, misoprostol, and placebo was 5%, 22%, and 3%, respectively.

Another study for the same indication, where patients took either a COX-2 inhibitor or lansoprazole and naproxen, demonstrated that the safety profile was similar to the prior study. Additional reactions from this study not previously observed in other clinical trials with PREVACID included contusion, duodenitis, epigastric discomfort, esophageal disorder, fatigue, hunger, hiatal hernia, hoarseness, impaired gastric emptying, metaplasia, and renal impairment.

Additional adverse experiences occurring in less than 1% of patients or subjects who received PREVACID in domestic trials are shown below:

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain

Cardiovascular System - angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation

Digestive System – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis

Endocrine System - diabetes mellitus, goiter, hypothyroidism

Hemic and Lymphatic System - anemia, hemolysis, lymphadenopathy

Metabolic and Nutritional Disorders - gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss

Musculoskeletal System - arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis

Nervous System – abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo

Respiratory System - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor

Skin and Appendages - acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria

Special Senses – abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect

Urogenital System - abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

6.2 Postmarketing Experience

Additional adverse experiences have been reported since PREVACID has been marketed. The majority of these cases are foreign-sourced and a relationship to PREVACID has not been established. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

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Body as a Whole – anaphylactic/anaphylactoid reactions; ***Digestive System -*** hepatotoxicity, pancreatitis, vomiting; ***Hemic and Lymphatic System -*** agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; ***Musculoskeletal System -*** myositis; ***Skin and Appendages*** – severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); ***Special Senses -*** speech disorder; ***Urogenital System –*** interstitial nephritis, urinary retention.

6.3 Combination Therapy with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with PREVACID, amoxicillin, or clarithromycin.

Triple Therapy: PREVACID/amoxicillin/clarithromycin
The most frequently reported adverse reactions for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse reactions between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse reactions were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: PREVACID/amoxicillin
The most frequently reported adverse reactions for patients who received PREVACID three times daily plus amoxicillin three times daily dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse reactions were observed at significantly higher rates with PREVACID three times daily plus amoxicillin three times daily dual therapy than with PREVACID alone.

For information on adverse reactions with amoxicillin or clarithromycin, refer to their full prescribing information, ADVERSE REACTIONS sections.

6.4 Laboratory Values

The following changes in laboratory parameters in patients who received PREVACID were reported as adverse reactions:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, blood potassium increased, blood urea increased, crystal urine present, eosinophilia, hemoglobin decreased, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, increased gastrin levels and positive fecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) and 0.4% (11/2677) patients, who received placebo and PREVACID, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients who received PREVACID reported jaundice at any time during the study.

In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

For information on laboratory value changes with amoxicillin or clarithromycin, refer to their full prescribing information, ADVERSE REACTIONS sections.

7 DRUG INTERACTIONS

Drugs with pH-Dependent Absorption Kinetics
PREVACID causes long-lasting inhibition of gastric acid secretion. PREVACID and other PPIs are likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, PREVACID and other PPIs should not be co-administered with atazanavir. ***[See Clinical Pharmacology (12.5)]***

It is theoretically possible that PREVACID and other PPIs may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole). ***[See Clinical Pharmacology (12.5)]***

Warfarin
In a study of healthy subjects, co-administration of single or multiple 60 mg doses of PREVACID and warfarin did not affect the pharmacokinetics of warfarin nor prothrombin time (***see Clinical Pharmacology (12.5)***. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. ***[See Clinical Pharmacology (12.5)]***

Theophylline
A minor increase (10%) in the clearance of theophylline was observed following the administration of PREVACID concomitantly with theophylline. Although the magnitude of the effect on theophylline clearance is small, individual patients may require additional titration of their theophylline dosage when PREVACID is started or stopped to ensure clinically effective blood levels. ***[See Clinical Pharmacology (12.5)]***

For information on drug interactions for amoxicillin or clarithromycin, refer to their full prescribing information, DRUG INTERACTIONS sections.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects
Pregnancy Category B. Reproduction studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day [49 times the recommended human dose (30 mg/day) based on body surface area (BSA)] and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (19 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of

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human response, this drug should be used during pregnancy only if clearly needed.

See full prescribing information for clarithromycin before using in pregnant women.

8.3 Nursing Mothers

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of lansoprazole to the mother.

8.4 Pediatric Use

The safety and effectiveness of PREVACID have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis, however, PREVACID was not effective in patients with symptomatic GERD 1 month to less than 1 year of age in a multi-center, double-blind, placebo controlled study.

Neonate to less than 1 year of age

The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged less than 28 days and 1 to 11 months. Compared to healthy adults receiving 30 mg, neonates had higher exposure (mean weight-based normalized AUC values 2.04- and 1.88-fold higher at doses of 0.5 mg/kg/day and1 mg/kg/day, respectively). Infants aged ≤ 10 weeks had clearance and exposure values that were similar to neonates. Infants aged greater than 10 weeks who received 1 mg/kg/day had mean AUC values that were similar to adults who received a 30 mg dose.

Lansoprazole was not found to be effective in a U.S. and Polish 4 week multicenter, double-blind, placebo-controlled, parallel-group study of 162 patients between one month and less than 12 months of age with symptomatic GERD based on a medical history of crying/fussing/irritability associated with feedings who had not responded to conservative GERD management (i.e., non-pharmacologic intervention) for 7 to 14 days. Patients received lansoprazole as a suspension daily (0.2 to 0.3 mg/kg/day in infants ≤ 10 weeks of age or 1.0 to 1.5 mg/kg/day in infants greater than 10 weeks or placebo) for up to 4 weeks of double-blind treatment.

The primary efficacy endpoint was assessed by greater than 50% reduction from baseline in either the percent of feedings with a crying/fussing/irritability episode or the duration (minutes) of a crying/fussing/irritability episode within one hour after feeding.

There was no difference in the percentage of responders between the lansoprazole pediatric suspension group and placebo group (54% in both groups).

There were no adverse events reported in pediatric clinical studies (1 month to less than 12 months of age) that were not previously observed in adults.

Based on the results of the Phase 3 efficacy study, lansoprazole was not shown to be effective. Therefore, these results do not support the use of lansoprazole in treating symptomatic GERD in infants.

One to 11 years of age

In an uncontrolled, open-label, U.S. multicenter study, 66 pediatric patients (1 to 11 years of age) with GERD were assigned, based on body weight, to receive an initial dose of either PREVACID 15 mg daily if ≤ 30 kg or PREVACID 30 mg daily if greater than 30 kg administered for 8 to 12 weeks. The PREVACID dose was increased (up to 30 mg twice daily) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. At baseline 85% of patients had mild to moderate overall GERD symptoms (assessed by investigator interview), 58% had non-erosive GERD and 42% had erosive esophagitis (assessed by endoscopy).

After 8 to 12 weeks of PREVACID treatment, the intent-to-treat analysis demonstrated an approximate 50% reduction in frequency and severity of GERD symptoms.

Twenty-one of 27 erosive esophagitis patients were healed at 8 weeks and 100% of patients were healed at 12 weeks by endoscopy (Table 2).

Table 2: GERD symptom improvement and Erosive Esophagitis healing rates in pediatric patients age 1 to 11

GERD	Final Visit[a] % (n/N)
Symptomatic GERD	
Improvement in Overall GERD Symptoms[b]	76% (47/62[c])
Erosive Esophagitis	
Improvement in Overall GERD Symptoms[b]	81% (22/27)
Healing Rate	100% (27/27)

[a] At Week 8 or Week 12
[b] Symptoms assessed by patients diary kept by caregiver.
[c] No data were available for 4 pediatric patients.

In a study of 66 pediatric patients in the age group 1 year to 11 years old after treatment with PREVACID given orally in doses of 15 mg daily to 30 mg twice daily, increases in serum gastrin levels were similar to those observed in adult studies. Median fasting serum gastrin levels increased 89% from 51 pg/ mL at baseline to 97 pg/mL [interquartile range (25th-75th percentile) of 71-130 pg/ mL] at the final visit.

The pediatric safety of PREVACID Delayed-Release Capsules has been assessed in 66 pediatric patients aged 1 to 11 years of age. Of the 66 patients with GERD 85% (56/66) took PREVACID for 8 weeks and 15% (10/66) took it for 12 weeks.

The most frequently reported (2 or more patients) treatment-related adverse reactions in patients 1 to 11 years of age (N=66) were constipation (5%) and headache (3%).

Twelve to 17 years of age

In an uncontrolled, open-label, U.S. multicenter study, 87 adolescent patients (12 to 17 years of age) with symptomatic GERD were treated with PREVACID for 8 to 12 weeks. Baseline upper endoscopies classified these patients into two groups: 64 (74%) nonerosive GERD and 23 (26%) erosive esophagitis (EE). The nonerosive GERD patients received PREVACID 15 mg daily for 8 weeks and the EE patients received PREVACID 30 mg daily for 8 to 12 weeks. At baseline, 89% of these patients had mild to moderate overall GERD symptoms (assessed by investigator interviews). During 8 weeks

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of PREVACID treatment, adolescent patients experienced a 63% reduction in frequency and a 69% reduction in severity of GERD symptoms based on diary results.

Twenty-one of 22 (95.5%) adolescent erosive esophagitis patients were healed after 8 weeks of PREVACID treatment. One patient remained unhealed after 12 weeks of treatment (Table 3).

Table 3: GERD symptom improvement and Erosive Esophagitis healing rates in pediatric patients age 12 to 17

GERD	Final Visit % (n/N)
Symptomatic GERD (All Patients)	
Improvement in Overall GERD Symptoms[a]	73.2% (60/82)[b]
Nonerosive GERD	
Improvement in Overall GERD Symptoms[a]	71.2% (42/59)[b]
Erosive Esophagitis	
Improvement in Overall GERD Symptoms[a]	78.3% (18/23)
Healing Rate[c]	95.5% (21/22)[c]

[a]Symptoms assessed by patient diary (parents/caregivers as necessary).
[b]No data available for 5 patients.
[c]Data from one healed patient was excluded from this analysis due to timing of final endoscopy.

In these 87 adolescent patients, increases in serum gastrin levels were similar to those observed in adult studies, median fasting serum gastrin levels increased 42% from 45 pg/mL at baseline to 64 pg/mL [interquartile range (25th – 75th percentile) of 44 – 88 pg/mL] at the final visit. (Normal serum gastrin levels are 25 to 111 pg/mL).

The safety of PREVACID Delayed-Release Capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients with GERD, 6% (5/87) took PREVACID for less than 6 weeks, 93% (81/87) for 6-10 weeks, and 1% (1/87) for greater than 10 weeks.

The most frequently reported (at least 3%) treatment-related adverse reactions in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this package insert as occurring in less than 1% of adult patients, was reported in this study by 3 adolescent patients with nonerosive GERD, who had dizziness concurrently with other reactions (such as migraine, dyspnea, and vomiting).

8.5 Geriatric Use

No dosage adjustment of PREVACID is necessary in geriatric patients. The incidence rates of PREVACID-associated adverse reactions and laboratory test abnormalities are similar to those seen in younger patients. ***[See Clinical Pharmacology (12.4)]***

8.6 Renal Impairment

No dosage adjustment of PREVACID is necessary in patients with renal impairment. The pharmacokinetics of lansoprazole in patients with various degrees of renal impairment were not substantially different compared to those in subjects with normal renal function. ***[See Clinical Pharmacology (12.4)]***

8.7 Hepatic Impairment

In patients with various degrees of chronic hepatic impairment, an increase in the mean AUC of up to 500% was observed at steady state compared to healthy subjects. Consider dose reduction in patients with severe hepatic impairment. ***[See Clinical Pharmacology (12.4)]***

8.8 Gender

Over 4,000 women were treated with PREVACID. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse reactions in females were similar to those seen in males. ***[See Clinical Pharmacology (12.4)]***

8.9 Race

The pooled mean pharmacokinetic parameters of PREVACID from twelve U.S. Phase 1 studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of PREVACID in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The C_{max} values were comparable.

10 OVERDOSAGE

PREVACID is not removed from the circulation by hemodialysis. In one reported overdose, a patient consumed 600 mg of PREVACID with no adverse reaction. Oral PREVACID doses up to 5000 mg/kg in rats (approximately 1600 times the 30 mg human dose based on BSA) and in mice (about 800 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

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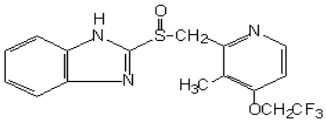
11 DESCRIPTION

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. 3*, 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, aspartame **, 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.

* PREVACID 15-mg capsules only.

** **Phenylketonurics: Contains Phenylalanine 2.5 mg per 15 mg Tablet and 5.1 mg per 30 mg Tablet.**

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PREVACID (lansoprazole) belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

12.2 Pharmacodynamics

Antisecretory Activity: After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was greater than 3 and greater than 4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

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The intragastric pH results of a five-day, pharmacodynamic, crossover study of 15 mg and 30 mg of once daily lansoprazole are presented in Table 4:

Table 4: Mean Antisecretory Effects After Single and Multiple Daily PREVACID Dosing

Parameter	Baseline Value	PREVACID 15 mg Day 1	PREVACID 15 mg Day 5	PREVACID 30 mg Day 1	PREVACID 30 mg Day 5
Mean 24-Hour pH	2.1	2.7[+]	4.0[+]	3.6[*]	4.9[*]
Mean Nighttime pH	1.9	2.4	3.0[+]	2.6	3.8[*]
% Time Gastric pH>3	18	33[+]	59[+]	51[*]	72[*]
% Time Gastric pH>4	12	22[+]	49[+]	41[*]	66[*]

NOTE: An intragastric pH of greater than 4 reflects a reduction in gastric acid by 99%.

[*](p<0.05) versus baseline and lansoprazole 15 mg.

[+](p<0.05) versus baseline only.

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with 30 mg of lansoprazole and 2-3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1-2 hours post-dosing with 15 mg of lansoprazole.

Acid suppression may enhance the effect of antimicrobials in eradicating ***Helicobacter pylori*** (***H. pylori***). The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of PREVACID given daily, twice daily and three times daily (Table 5).

Table 5: Mean Antisecretory Effects After 5 Days of twice daily and three times daily Dosing

Parameter	PREVACID 30 mg daily	PREVACID 15 mg twice daily	PREVACID 30 mg twice daily	PREVACID 30 mg three times daily
% Time Gastric pH>5	43	47	59[+]	77[*]
% Time Gastric pH>6	20	23	28	45[*]

[+](p<0.05) versus PREVACID 30 mg daily

[*](p<0.05) versus PREVACID 30 mg daily, 15 mg twice daily and 30 mg twice daily.

The inhibition of gastric acid secretion as measured by intragastric pH gradually returned to normal over two to four days after multiple doses. There was no indication of rebound gastric acidity.

Enterochromaffin-like (ECL) Cell Effects

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole. ***[See Nonclinical Toxicology (13.1)]***

Other Gastric Effects in Humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects

In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 to 60 mg of oral lansoprazole. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy.

Endocrine Effects

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function. In 24-month carcinogenicity studies in Sprague-Dawley rats with daily lansoprazole dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rats.

Other Effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems have been found in humans. Among 56 patients who had extensive baseline eye evaluations, no visual toxicity was observed after lansoprazole treatment (up

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to 180 mg/day) for up to 58 months. After lifetime lansoprazole exposure in rats, focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy were seen.

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. ***[See Indications and Usage (1.2)]***

Helicobacter pylori Pretreatment Resistance

Clarithromycin pretreatment resistance (≥2.0 µg/mL) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (≤0.25 µg/mL) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one of 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of greater than 0.25 µg/mL. One patient on the 14-day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of greater than 256 µg/mL by E-test and the patient was eradicated of ***H. pylori*** (Table 6)**.**

Table 6: Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a]

Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results			
		H. pylori negative – eradicated	***H. pylori*** positive – not eradicated		
			Post-treatment susceptibility results		
			S[b]	I[b]	R[b]	No MIC
Triple Therapy 14-Day (lansoprazole 30 mg twice daily /amoxicillin 1 gm twice daily /clarithromycin 500 mg twice daily) (M95-399, M93-131, M95-392)						
Susceptible[b]	112	105				7
Intermediate[b]	3	3				
Resistant[b]	17	6			7	4
Triple Therapy 10-Day (lansoprazole 30 mg twice daily /amoxicillin 1 gm twice daily /clarithromycin 500 mg twice daily) (M95-399)						
Susceptible[b]	42	40	1		1	
Intermediate[b]						
Resistant[b]	4	1			3	

[a]Includes only patients with pretreatment clarithromycin susceptibility test results
[b]Susceptible (S) MIC ≤0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥2 µg/mL

Patients not eradicated of ***H. pylori*** following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant ***H. pylori.*** Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant ***H. pylori*** should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes: In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤0.25 µg/mL) were eradicated of ***H. pylori***. Of those with pretreatment amoxicillin MICs of greater than 0.25 µg/mL, three of six had the ***H. pylori*** eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg three times daily /amoxicillin 1 gm three times daily dual therapy and a total of 12.8% (22/172) of the patients failed the 10- and 14-day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant ***H. pylori*** isolates.

Susceptibility Test for Helicobacter pylori: The reference methodology for susceptibility testing of ***H. pylori*** is agar dilution MICs.[1] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard ($1 \times 10^7 – 1 \times 10^8$ CFU/mL for ***H. pylori***) are inoculated directly onto freshly prepared antimicrobial-containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters.

After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria (Table 7):

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Table 7	
Clarithromycin MIC (µg/mL)[a]	Interpretation
≤0.25	Susceptible (S)
0.5-1.0	Intermediate (I)
≥2.0	Resistant (R)
Amoxicillin MIC (µg/mL)[b]	Interpretation
≤0.25	Susceptible (S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
[b] There were not enough organisms with MICs greater than 0.25 µg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values (Table 8):

Table 8		
Microorganism	Antimicrobial Agent	MIC (µg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.015-0.12 µg/mL
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 µg/mL

[a]These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

12.3 Pharmacokinetics

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 plasma concentrations (C_{max}) of lansoprazole and the area under the plasma concentration curves (AUCs) of lansoprazole were approximately proportional to the administered dose. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption: The absorption of lansoprazole is rapid, with the mean C_{max} occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both the C_{max} and AUC are diminished by about 50% to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if lansoprazole is given before meals.

Distribution: Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 µg/mL.

Metabolism: Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [(H^+, K^+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Elimination: Following single-dose oral administration of PREVACID, virtually no unchanged lansoprazole was excreted in the urine. In one study, 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 feces. This implies a significant biliary excretion of the lansoprazole metabolites.

12.4 Specific Populations

Pediatric Use:
One to 17 years of age
The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged 1 to 11 years and 12 to 17 years in two separate clinical studies. In children aged 1 to 11 years, lansoprazole was dosed 15 mg daily for subjects weighing ≤ 30 kg and 30 mg daily for subjects weighing greater than 30 kg. Mean C_{max} and AUC values observed on Day 5 of dosing were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in the study. In adolescent subjects aged 12 to 17 years, subjects were randomized to receive lansoprazole at 15 mg or 30 mg daily. Mean C_{max} and AUC values of lansoprazole were not affected by body weight or age; and nearly dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, lansoprazole pharmacokinetics in pediatric patients aged 1 to 17 years were similar to those observed in healthy adult subjects.

Neonate to less than one year of age
Refer to Section 8.4 for the pharmacokinetics of lansoprazole in pediatric patients with GERD aged less than 28 days and 1 to 11 months.

Geriatric Use: The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly. No dosage adjustment is necessary in the elderly ***[See Use in Specific Populations (8.5)].***

Renal Impairment: In patients with severe renal impairment, plasma protein binding decreased by 1.0%-1.5% after administration of 60 mg of lansoprazole. Patients with renal impairment had a shortened elimination half-life and decreased total AUC (free and bound). The AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment; and the C_{max} and t_{max} (time to reach the maximum concentration) were not different than the C_{max} and t_{max} from subjects with normal renal function. No dosage adjustment is necessary in patients with renal impairment ***[See Use in Specific Populations (8.6)]***.

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Hepatic Impairment: In patients with various degrees of chronic hepatic impairment, the mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in the mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Consider dose reduction in patients with severe hepatic impairment ***[See Use in Specific Populations (8.7)].***

Gender: In a study comparing 12 male and 6 female human subjects who received lansoprazole, no gender differences were found in pharmacokinetics and intragastric pH results ***[See Use in Specific Populations (8.5)]***.

12.5 Drug-Drug Interactions

It is theoretically possible that PREVACID may interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

PREVACID is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that PREVACID does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

Atazanavir: PREVACID causes long-lasting inhibition of gastric acid secretion. PREVACID substantially decreases the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, PREVACID, or other proton pump inhibitors, should not be co-administered with atazanavir.

Theophylline: When PREVACID was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when PREVACID is started or stopped to ensure clinically effective blood levels.

Warfarin: In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including PREVACID, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Methotrexate and 7-hydromethotrexate: In an open-label, single-arm, eight-day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg twice daily and PREVACID 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse reactions were noted.

Amoxicillin: PREVACID has also been shown to have no clinically significant interaction with amoxicillin.

Sucralfate: In a single-dose crossover study examining PREVACID 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID and there was no evidence of a change in the efficacy of PREVACID.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole doses of 5 to 150 mg/kg/day - about 1.6 to 49 times the recommended human dose of (30 mg/day) on a body surface area (BSA) basis. Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (5 to 49 times the recommended human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. In addition, in a one-year toxicity study, testicular interstitial cell adenoma occurred in 1 of 30 rats treated with 50 mg/kg/day of lansoprazole (16 times the recommended human dose based on BSA).

In a 24-month carcinogenicity study, CD-1 mice were treated with oral lansoprazole doses of 15 to 600 mg/kg/day, 2 to 97 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (49 to 97 times the recommended human dose based on BSA) and female mice treated with 150 to 600 mg/kg/day (24 to 97 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (12 to 97 times the recommended human dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Lansoprazole was not genotoxic in the Ames test, the ***ex vivo*** rat hepatocyte unscheduled DNA synthesis (UDS) test, the ***in vivo*** mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test. It was positive in ***in vitro*** human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (49 times the recommended human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

Duodenal Ulcer

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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 9).

Table 9: Duodenal Ulcer Healing Rates				
	PREVACID			Placebo
Week	15 mg daily (N=68)	30 mg daily (N=74)	60 mg daily (N=70)	(N=72)
2	42.4%*	35.6%*	39.1%*	11.3%
4	89.4%*	91.7%*	89.9%*	46.1%

* ($p \leq 0.001$) versus placebo.

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 10). ***[See Indications and Usage (1.1)]***

Table 10: Duodenal Ulcer Healing Rates				
	PREVACID		Ranitidine	Placebo
Week	15 mg daily (N=80)	30 mg daily (N=77)	300 mg h.s. (N=82)	(N=41)
2	35.0%	44.2%	30.5%	34.2%
4	92.3%**	80.3%*	70.5%*	47.5%

*($p \leq 0.05$) versus placebo.

**($p \leq 0.05$) versus placebo and ranitidine.

***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 twice daily / amoxicillin 1 gm twice daily / clarithromycin 500 mg twice daily
Dual therapy: PREVACID 30 mg three times daily / amoxicillin 1 gm three times daily

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 11 and 12)***. [See Indications and Usage (1.2)]***

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Table 11
H. pylori Eradication Rates – Triple Therapy
(PREVACID/amoxicillin/clarithromycin)
Percent of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Duration	Triple Therapy Evaluable Analysis*	Triple Therapy Intent-to-Treat Analysis#
M93-131	14 days	92† [80.0-97.7] (N=48)	86† [73.3-93.5] (N=55)
M95-392	14 days	86‡ [75.7-93.6] (N=66)	83‡ [72.0-90.8] (N=70)
M95-399+	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)

*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 dropped out of the study due to an adverse event related to the study drug, they were included in the evaluable analysis as failures of therapy.

#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 therapy.
†($p<0.05$) versus PREVACID/amoxicillin and PREVACID/clarithromycin dual therapy.
‡($p<0.05$) versus clarithromycin/amoxicillin dual therapy.
+The 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.

Table 12
H. pylori Eradication Rates – 14-Day Dual Therapy
(PREVACID/amoxicillin)
Percent of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Dual Therapy Evaluable Analysis*	Dual Therapy Intent-to-Treat Analysis#
M93-131	77† [62.5-87.2] (N=51)	70† [56.8-81.2] (N=60)
M93-125	66‡ [51.9-77.5] (N=58)	61‡ [48.5-72.9] (N=67)

* 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 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.
# 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 therapy.
† ($p<0.05$) versus PREVACID alone.
‡ ($p<0.05$) versus PREVACID alone or amoxicillin alone.

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 13). ***[See Indications and Usage (1.3)]***

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Table 13: Endoscopic Remission Rates					
Trial	Drug	No. of Pts.	Percent in Endoscopic Remission		
			0-3 mo.	0-6 mo.	0-12 mo.
#1	PREVACID 15 mg daily	86	90%*	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
*($p \leq 0.001$) versus placebo.

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 14). ***[See Indications and Usage (1.4)]***

Table 14: Gastric Ulcer Healing Rates				
	PREVACID			Placebo
Week	15 mg daily (N=65)	30 mg daily (N=63)	60 mg daily (N=61)	(N=64)
4	64.6%*	58.1%*	53.3%*	37.5%
8	92.2%*	96.8%*	93.2%*	76.7%

* ($p \leq 0.05$) versus placebo.

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 NSAID-associated gastric ulcer who continued their NSAID use, the percentage of patients healed after 8 weeks was statistically significantly higher with 30 mg of PREVACID than with the active control. A total of 711 patients were enrolled in the study, and 701 patients were treated. Patients ranged in age from 18 to 88 years (median age 59 years), with 67% 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 15). ***[See Indications and Usage (1.5)]***

Table 15: NSAID-Associated Gastric Ulcer Healing Rates [1]		
Study #1		
	PREVACID 30 mg daily	Active Control [2]
Week 4	60% (53/88) [3]	28% (23/83)
Week 8	79% (62/79) [3]	55% (41/74)
Study #2		
	PREVACID 30 mg daily	Active Control [2]
Week 4	53% (40/75)	38% (31/82)
Week 8	77% (47/61) [3]	50% (33/66)

[1]Actual observed ulcer(s) healed at time points $\pm$ 2 days

[2]Dose for healing of gastric ulcer

[3]($p \leq 0.05$) versus the active control

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 16). ***[See Indications and Usage (1.6)]***

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Table 16: Proportion of Patients Remaining Free of Gastric Ulcers[1]				
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%

[1]% = 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.

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 17 and in Figures 1 and 2:

Table 17: 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%*	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%*

*(p<0.01) versus placebo.

Figure 1

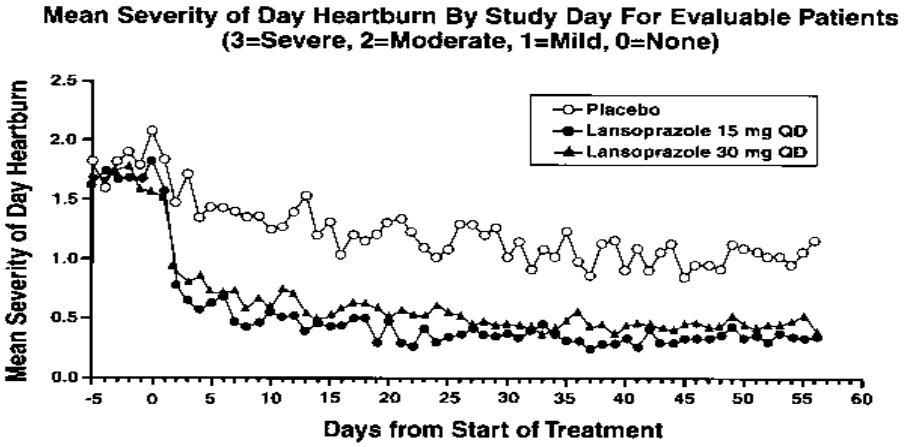

Figure 2

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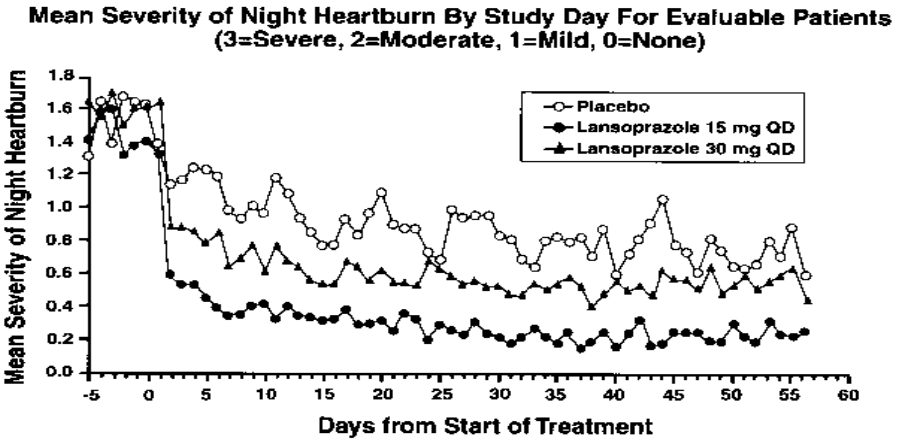

In two U.S., multicenter double-blind, ranitidine-controlled studies of 925 total patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, lansoprazole 15 mg was superior to ranitidine 150 mg (twice daily) in decreasing the frequency and severity of day and night heartburn associated with GERD for the 8-week treatment period. No significant additional benefit from lansoprazole 30 mg once daily was observed. ***[See Indications and Usage (1.7)]***

Erosive Esophagitis

In a U.S. multicenter, double-blind, placebo-controlled study of 269 patients entering with an endoscopic diagnosis of esophagitis with mucosal grading of 2 or more and grades 3 and 4 signifying erosive disease, the percentages of patients with healing are presented in Table 18:

Table 18: Erosive Esophagitis Healing Rates				
	PREVACID			Placebo
	15 mg daily	30 mg daily	60 mg daily	
Week	(N=69)	(N=65)	(N=72)	(N=63)
4	67.6%*	81.3%*†	80.6%*†	32.8%
6	87.7%*	95.4%*	94.3%*	52.5%
8	90.9%*	95.4%*	94.4%*	52.5%

* ($p \leq 0.001$) versus placebo.
† ($p \leq 0.05$) versus PREVACID 15 mg.

In this study, all PREVACID groups reported significantly greater relief of heartburn and less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets taken per day than the placebo group.
Although all doses were effective, the earlier healing in the higher two doses suggests 30 mg daily as the recommended dose.

PREVACID was also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflux esophagitis. PREVACID at a dose of 30 mg was significantly more effective than ranitidine 150 mg twice daily as shown below (Table 19).

Table 19: Erosive Esophagitis Healing Rates		
Week	PREVACID 30 mg daily (N=115)	Ranitidine 150 mg twice daily (N=127)
2	66.7%*	38.7%
4	82.5%*	52.0%
6	93.0%*	67.8%
8	92.1%*	69.9%

*($p \leq 0.001$) versus ranitidine.

In addition, patients treated with PREVACID reported less day and nighttime heartburn and took less antacid tablets for fewer days than patients taking ranitidine 150 mg twice daily.

Although this study demonstrates effectiveness of PREVACID in healing erosive esophagitis, it does not represent an adequate comparison with ranitidine because the recommended ranitidine dose for esophagitis is 150 mg q.i.d., twice the dose used in this study.

In the two trials described and in several smaller studies involving patients with moderate to severe erosive esophagitis, PREVACID produced healing rates similar to those shown above.

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACID was compared with ranitidine 150 mg twice daily in 151 patients with erosive reflux esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least one H_2-receptor antagonist given at the dose indicated for symptom relief or greater, namely, cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidine 300 mg/day.

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PREVACID 30 mg was more effective than ranitidine 150 mg twice daily in healing reflux esophagitis, and the percentage of patients with healing were as follows. This study does not constitute a comparison of the effectiveness of histamine H_2-receptor antagonists with PREVACID, as all patients had demonstrated unresponsiveness to the histamine H_2-receptor antagonist mode of treatment. It does indicate, however, that PREVACID may be useful in patients failing on a histamine H_2-receptor antagonist (Table 20). ***[See Indications and Usage (1.7)]***

Table 20: Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H_2-Receptor Antagonist Therapy

Week	PREVACID 30 mg daily (N=100)	Ranitidine 150 mg twice daily (N=51)
4	74.7%*	42.6%
8	83.7%*	32.0%

*($p \leq 0.001$) versus ranitidine.

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 21).

Table 21: 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	59	83%*	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
*($p \leq 0.001$) versus placebo.

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 twice daily (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. ***[See Indications and Usage (1.8)]***

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome (ZES) 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 (2.1)]*** PREVACID was well tolerated at these high dose levels for prolonged periods (greater than four years in some patients). In most ZES 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. ***[See Indications and Usage (1.9)]***

15 REFERENCE

1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL, January 11-13, 1998.

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16 HOW SUPPLIED/STORAGE AND HANDLING

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored pink and green with the "TAP" and "PREVACID 15" imprinted on the capsules. The 30 mg capsules are opaque, hard gelatin, colored pink and black with the "TAP" and "PREVACID 30" imprinted on the capsules. They are available as follows:

NDC 64764-541-30 Unit of use bottles of 30: 15-mg capsules
NDC 64764-541-19 Bottles of 1000: 15-mg capsules
NDC 64764-541-11 Unit dose package of 100: 15-mg capsules
NDC 64764-046-13 Bottles of 100: 30-mg capsules
NDC 64764-046-19 Bottles of 1000: 30-mg capsules
NDC 64764-046-11 Unit dose package of 100: 30-mg capsules

PREVACID for Delayed-Release Oral Suspension contains white to pale brownish lansoprazole granules and inactive pink granules in a unit dose packet. They are available as follows:

NDC 64764-309-30 Unit dose carton of 30: 15-mg packets
NDC 64764-311-30 Unit dose carton of 30: 30-mg packets

PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets, 15 mg, are white to yellowish white uncoated tablets with orange to dark brown speckles, with "15" debossed on one side of the tablet. The 30 mg are white to yellowish white uncoated tablets with orange to dark brown speckles, with "30" debossed on one side of the tablet. The tablets are available as follows:

NDC 64764-543-11 Unit dose packages of 100: 15-mg tablets
NDC 64764-544-11 Unit dose packages of 100: 30-mg tablets

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

Patient should be informed of the following:

17.1 Information for Patients

PREVACID is available as a capsule, orally disintegrating tablet and oral suspension, and is available in 15 mg and 30 mg strengths. Directions for use specific to the route and available methods of administration for each of these dosage forms is presented below. ***[See Dosage and Administration (2.3)]***

- PREVACID should be taken before eating.
- PREVACID products SHOULD NOT BE CRUSHED OR CHEWED.
- **Phenylketonurics: Contains Phenylalanine 2.5 mg per 15 mg Tablet and 5.1 mg per 30 mg Tablet.**

Administration Options

1 PREVACID Delayed-Release Capsules

- PREVACID Delayed-Release Capsules should be swallowed whole.
- Alternatively, for patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened and administered as follows:
  - Open capsule.
  - Sprinkle intact granules on one tablespoon of either applesauce, ENSURE® pudding, cottage cheese, yogurt or strained pears.
  - Swallow immediately.
- PREVACID Delayed-Release Capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:
  - Open capsule.
  - Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 mL – approximately 2 ounces).
  - Mix briefly.
  - Swallow immediately.
  - To ensure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

2 PREVACID SoluTab Delayed-Release Orally Disintegrating Tablets

- PREVACID SoluTab should not be chewed.
  - Place the tablet on the tongue and allow it to disintegrate, with or without water, until the particles can be swallowed.
  - The tablet typically disintegrates in less than 1 minute.
- Alternatively, for children or other patients who have difficulty swallowing tablets, PREVACID SoluTab can be delivered in two different ways.

  PREVACID SoluTab – Oral Syringe

  For administration via oral syringe, PREVACID SoluTab can be administered as follows:
  - Place a 15 mg tablet in oral syringe and draw up approximately 4 mL of water, or place a 30 mg tablet in oral syringe and draw up approximately 10 mL of water.
  - Shake gently to allow for a quick dispersal.
  - After the tablet has dispersed, administer the contents within 15 minutes.
  - Refill the syringe with approximately 2 mL (5 mL for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

  PREVACID SoluTab – Nasogastric Tube Administration (≥ 8 French)

  For administration via a nasogastric tube, PREVACID SoluTab can be administered as follows:
  - Place a 15 mg tablet in a syringe and draw up 4 mL of water, or place a 30 mg tablet in a syringe and draw up 10 mL of water.
  - Shake gently to allow for a quick dispersal.
  - After the tablet has dispersed, inject through the nasogastric tube into the stomach within 15 minutes.
  - Refill the syringe with approximately 5 mL of water, shake gently, and flush the nasogastric tube.

3 ***PREVACID for Delayed-Release Oral Suspension***

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

PREVACID for Delayed-Release Oral Suspension should be administered as follows:

- Open packet.
- To prepare a dose, empty the packet contents into a container containing 2 tablespoons of **WATER**. DO NOT USE OTHER LIQUIDS OR FOODS.
- Stir well, and drink immediately.
- If any material remains after drinking, add more water, stir, and drink immediately.
- **This product should not be given through enteral administration tubes.**

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