

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### Lansoprazole Delayed-release Capsules

For oral administration Initial U.S. Approval: 1995

#### RECENT MAJOR CHANGES

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

#### INDICATIONS AND USAGE

Lansoprazole delayed-release capsules are a proton pump inhibitor (PPI). Refer to DOSAGE and ADMINISTRATION table (below) for indications and usage.

#### DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
<b>Duodenal Ulcers (1.1, 1.3)</b>		
Short-Term Treatment	15 mg	Once daily for 4 wks
Maintenance of Healed	15 mg	Once daily
<b>Benign Gastric Ulcer Short-Term Treatment (1.4)</b>		
Healing Risk Reduction	30 mg	Once daily up to 8 wks
<b>NSAID-associated Gastric Ulcer (1.6)</b>		
Healing Risk Reduction	30 mg	Once daily for 8 wks
	15 mg	Once daily up to 12 wks
<b>GERD (1.7)</b>		
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
<b>Pediatric (8.4)</b>		
(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

Continued

Indication	Dose	Frequency
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: 15 mg and 30 mg. (3)

#### CONTRAINDICATIONS

Contraindicated in patients with known severe hypersensitivity to any component of the lansoprazole delayed-release capsules formulation. (4)

#### WARNINGS AND PRECAUTIONS

Symptomatic response with lansoprazole 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 Mylan Pharmaceuticals Inc. at 1-877-4-INFO-RX. (1-877-446-3679) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Do not coadminister 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)
- Concomitant tacrolimus use may increase tacrolimus whole blood concentrations. (7)
- Titration of theophylline dosage may be required when concomitant lansoprazole 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.

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LANS:R1

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## 1 INDICATIONS AND USAGE

### 1.1 Short-Term Treatment of Active Duodenal Ulcer

Lansoprazole delayed-release capsules are indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer. [See Clinical Studies (14).]

### 1.3 Maintenance of Healed Duodenal Ulcers

Lansoprazole delayed-release capsules are 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

Lansoprazole delayed-release capsules are 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

Lansoprazole delayed-release capsules are 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

Lansoprazole delayed-release capsules are 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

Lansoprazole delayed-release capsules are indicated for the treatment of heartburn and other symptoms associated with GERD. [See Clinical Studies (14).]

#### Short-Term Treatment of Erosive Esophagitis

Lansoprazole delayed-release capsules are 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 lansoprazole delayed-release capsules for 8 weeks (5% to 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 lansoprazole delayed-release capsules may be considered. [See Clinical Studies (14).]

#### 1.8 Maintenance of Healing of Erosive Esophagitis (EE)

Lansoprazole delayed-release capsules are 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

Lansoprazole delayed-release capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. [See Clinical Studies (14).]

## 2 DOSAGE AND ADMINISTRATION

Lansoprazole delayed-release capsules are available as capsules in 15 mg and 30 mg strengths. Lansoprazole delayed-release capsules should be taken before eating. Lansoprazole delayed-release capsules SHOULD NOT BE CRUSHED OR CHEWED. In the clinical trials, antacids were used concomitantly with lansoprazole.

### 2.1 Recommended Dose

Indication	Recommended Dose	Frequency
<b>Duodenal Ulcers</b>		
Short-Term Treatment	15 mg	Once daily for 4 weeks
Maintenance of Healed	15 mg	Once daily
<b>Benign Gastric Ulcer</b>		
Short-Term Treatment	30 mg	Once daily for up to 8 weeks
<b>NSAID-associated Gastric Ulcer</b>		
Healing	30 mg	Once daily for 8 weeks*
Risk Reduction	15 mg	Once daily for up to 12 weeks**
<b>Gastroesophageal Reflux Disease (GERD)</b>		
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**
<b>Pediatric</b>		
<b>(1 to 11 years of age)</b>		
<b>Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of Erosive Esophagitis</b>		
≤ 30 kg	15 mg	Once daily for up to 12 weeks+
> 30 kg	30 mg	Once daily for up to 12 weeks+
<b>(12 to 17 years of age)</b>		
<b>Short-Term Treatment of Symptomatic GERD</b>		
Nonerosive GERD	15 mg	Once daily for up to 8 weeks
Erosive Esophagitis	30 mg	Once daily for up to 8 weeks
<b>Maintenance of Healing of Erosive Esophagitis</b>	15 mg	Once daily
<b>Pathological Hypersecretory Conditions</b>		
<b>Including Zollinger-Ellison Syndrome</b>	60 mg	Once daily***

\* Controlled studies did not extend beyond indicated duration.

\*\* For patients who do not heal with lansoprazole for 8 weeks (5% to 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 lansoprazole 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 lansoprazole for more than 4 years.

+ The lansoprazole 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

##### Lansoprazole Delayed-release Capsules -Oral Administration

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

##### Lansoprazole Delayed-release Capsules -Nasogastric Tube Administration

- For patients who have a nasogastric tube in place, lansoprazole delayed-release capsules can be administered as follows:
  - Open capsule.
  - Mix intact pellets 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.

### 3 DOSAGE FORMS AND STRENGTHS

- 15 mg capsules have a green opaque cap, green opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with **MYLAN** over **8015** in black ink on both the cap and body.
- 30 mg capsules pink opaque cap, pink opaque body, hard-shell gelatin capsule filled with white to off-white pellets. The capsule is axially printed with **MYLAN** over **8030** in black ink on both the cap and the body.

## 4 CONTRAINDICATIONS

Lansoprazole delayed-release capsules are contraindicated in patients with known severe hypersensitivity to any component of the formulation of lansoprazole.

## 5 WARNINGS AND PRECAUTIONS

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

## 6 ADVERSE REACTIONS

### 6.1 Clinical

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for lansoprazole delayed-release capsules and lansoprazole for delayed-release oral suspension are similar. In general, lansoprazole 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 lansoprazole-treated patients and occurred at a greater rate in lansoprazole-treated patients than placebo-treated patients in Table 1.

Body System/Adverse Event	Lansoprazole (N = 2,768) %	Placebo (N = 1,023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1	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 lansoprazole, but higher in the patients who received 60 mg of lansoprazole (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 lansoprazole for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with lansoprazole, 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 lansoprazole 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 lansoprazole 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, gastrointestinal 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:** avitaminosis, gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss

**Musculoskeletal System:** arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, ptosis, synovitis

**Nervous System:** abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, dementia, 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, lung fibrosis, 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, amblyopia, blepharitis, blurred vision, cataract, conjunctivitis, deafness, dry eyes, ear/eye disorder, eye pain, glaucoma, otitis media, parosmia, photophobia, retinal degeneration/disorder, 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 retention, urinary tract infection, urinary urgency, urination impaired, vaginitis

## 6.2 Post-Marketing Experience

Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole 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.

**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

## 6.4 Laboratory Values

The following changes in laboratory parameters in patients who received lansoprazole 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% (11/2,677) patients, who received placebo and lansoprazole, respectively, had enzyme elevations greater than 3 times the upper limit of normal range at the final treatment visit. None of these patients who received lansoprazole reported jaundice at any time during the study.

## 7 DRUG INTERACTIONS

### Drugs with pH-Dependent Absorption Kinetics

Lansoprazole causes long-lasting inhibition of gastric acid secretion. Lansoprazole 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, lansoprazole and other PPIs should not be coadministered with atazanavir. [See *Clinical Pharmacology* (12.5).]

It is theoretically possible that lansoprazole 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, coadministration of single or multiple 60 mg doses of lansoprazole 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).]

### Tacrolimus

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

### Theophylline

A minor increase (10%) in the clearance of theophylline was observed following the administration of lansoprazole 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 lansoprazole is started or stopped to ensure clinically effective blood levels. [See *Clinical Pharmacology* (12.5).]

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Teratogenic effects

**Pregnancy Category B.** Reproduction studies have been performed in pregnant rats at oral doses up to 40 times the recommended human dose and in pregnant rabbits at oral doses up to 16 times the recommended human dose 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 human response, this drug should be used during pregnancy only if clearly needed [see *Non-clinical Toxicology* (13.2)].

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 lansoprazole have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis.

#### 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 lansoprazole 15 mg daily if  $\leq 30$  kg or lansoprazole 30 mg daily if greater than 30 kg administered for 8 to 12 weeks. The lansoprazole 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 lansoprazole 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).

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

<sup>a</sup> At Week 8 or Week 12

<sup>b</sup> Symptoms assessed by patients diary kept by caregiver.

<sup>c</sup> No data were available for four pediatric patients.

In a study of 66 pediatric patients in the age group 1 year to 11 years old after treatment with lansoprazole 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 (25<sup>th</sup> to 75<sup>th</sup> percentile) of 71 to 130 pg/mL] at the final visit.

The pediatric safety of lansoprazole 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 lansoprazole for 8 weeks and 15% (10/66) took it for 12 weeks.

The most frequently reported (two 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 lansoprazole 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 lansoprazole 15 mg daily for 8 weeks and the EE patients received lansoprazole 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 of lansoprazole 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 lansoprazole treatment. One patient remained unhealed after 12 weeks of treatment (Table 3).

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

<sup>a</sup>Symptoms assessed by patient diary (parents/caregivers as necessary).

<sup>b</sup>No data available for five patients.

<sup>c</sup>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 (25<sup>th</sup> to 75<sup>th</sup> percentile) of 44 to 88 pg/mL] at the final visit. (Normal serum gastrin levels are 25 to 111 pg/mL).

The safety of lansoprazole delayed-release capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients with GERD, 6% (5/87) took lansoprazole for less than 6 weeks, 93% (81/87) for 6 to 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 three 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 lansoprazole is necessary in geriatric patients. The incidence rates of lansoprazole-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 lansoprazole 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 lansoprazole. 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

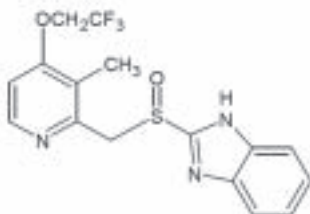
The pooled mean pharmacokinetic parameters of lansoprazole from 12 U.S. Phase 1 studies (N = 513) were compared to the mean pharmacokinetic parameters from two Asian studies (N = 20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The C<sub>max</sub> values were comparable.

## 10 OVERDOSAGE

Lansoprazole is not removed from the circulation by hemodialysis. In one reported overdose, a patient consumed 600 mg of lansoprazole with no adverse reaction. Oral lansoprazole doses up to 5000 mg/kg in rats [approximately 1,300 times the 30 mg human dose based on body surface area (BSA)] and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

## 11 DESCRIPTION

The active ingredient in lansoprazole delayed-release capsules, USP 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 molecular formula is C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S with a molecular weight of 369.37. Lansoprazole has the following structure:



Lansoprazole, USP 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 2 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.

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 pellets consisting of 15 mg or 30 mg of lansoprazole (active ingredient) and the following inactive ingredients: colloidal silicon dioxide, corn starch, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, magnesium carbonate, methacrylic acid copolymer, polyethylene glycol, polysorbate 80, sucrose, sugar spheres, talc and titanium dioxide. In addition, the 15 mg gelatin capsule contains FD&C Green No. 3 and FD&C Red No. 40; the 30 mg gelatin capsule contains Red Acid 18, FD&C Blue No. 1 and FD&C Red No 3; for both strengths the gelatin capsules contain gelatin and titanium dioxide.

The printing ink contains black iron oxide, propylene glycol, shellac and potassium hydroxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H<sup>+</sup>, K<sup>+</sup>)-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.

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:

Parameter	Baseline Value	Lansoprazole			
		15 mg		30 mg	
		Day 1	Day 5	Day 1	Day 5
Mean 24-Hour pH	2.1	2.7*	4*	3.6*	4.9*
Mean Nighttime pH	1.9	2.4	3*	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 to 2 hours with 30 mg of lansoprazole and 2 to 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 to 2 hours post-dosing with 15 mg of lansoprazole.

The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of lansoprazole 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	Lansoprazole			
	30 mg daily	15 mg twice daily	30 mg twice daily	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 lansoprazole 30 mg daily

+ (p < 0.05) versus lansoprazole 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 2 to 4 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 7 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 2,100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 mg to 60 mg of oral lansoprazole. These elevations reached a plateau within 2 months of therapy and returned to pretreatment levels within 4 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 somatotrophic hormone (STH). Lansoprazole in oral doses of 15 mg to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 mg to 60 mg for 2 to 8 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 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.

### 12.3 Pharmacokinetics

Lansoprazole delayed-release capsules contain an enteric-coated pellets formulation of lansoprazole. Absorption of lansoprazole begins only after the pellets 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<sub>max</sub>) 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<sub>max</sub> 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) hours. Both the C<sub>max</sub> 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 mcg/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<sup>+</sup>, K<sup>+</sup>)-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 lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of <sup>14</sup>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.

### 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% to 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)].

### 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 to 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 six 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 lansoprazole 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).

Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A.

### Atazanavir

Lansoprazole causes long-lasting inhibition of gastric acid secretion. Lansoprazole 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, Lansoprazole, or other proton pump inhibitors, should not be coadministered with atazanavir.

### Theophylline

When lansoprazole 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 lansoprazole 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 lansoprazole, 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, 8 day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 mg to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg twice daily and lansoprazole 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

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

### Sucralfate

In a single-dose crossover study examining lansoprazole 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 lansoprazole and there was no evidence of a change in the efficacy of lansoprazole.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole doses of 5 to 150 mg/kg/day -about 1 to 40 times the exposure on a body surface ( $\text{mg}/\text{m}^2$ ) basis of a 50-kg person of average height [1.46  $\text{m}^2$  body surface area (BSA)] given the recommended human dose of 30 mg/day. 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 (4 to 40 times the recommended human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24-month carcinogenicity study, CD-1 mice were treated with oral lansoprazole doses of 15 to 600 mg/kg/day, 2 to 80 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 (40 to 80 times the recommended human dose based on BSA) and female mice treated with 150 to 600 mg/kg/day (20 to 80 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 (10 to 80 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 (40 times the recommended human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

### 13.2 Animal Toxicology and/or Pharmacology

#### Reproductive Toxicology Studies

Reproduction studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day [40 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 (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

## 14 CLINICAL STUDIES

### Duodenal Ulcer

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15 mg, 30 mg and 60 mg of lansoprazole once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after 2 and 4 weeks was significantly higher with all doses of lansoprazole than with placebo. There was no evidence of a greater or earlier response with the two higher doses compared with lansoprazole 15 mg. Based on this study and the second study described below, the recommended dose of lansoprazole in duodenal ulcer is 15 mg per day (Table 6).

	Lansoprazole			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.

Lansoprazole 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 mg and 30 mg of lansoprazole once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after 4 weeks was significantly higher with both doses of lansoprazole than with placebo. There was no evidence of a greater or earlier response with the higher dose of lansoprazole. Although the 15 mg dose of lansoprazole 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 lansoprazole and ranitidine leaves the comparative effectiveness of the two agents undetermined (Table 7). [See Indications and Usage (1.1).]

	Lansoprazole		Ranitidine	Placebo
Week	15 mg daily (N = 80)	30 mg daily (N = 77)	300 mg h.s. (N = 82)	(N = 41)
2	35%	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.

### Long-Term Maintenance Treatment of Duodenal Ulcers

Lansoprazole 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 lansoprazole than in patients treated with placebo over a 12 month period (Table 8). [See Indications and Usage (1.3).]

Trial	Drug	No. of Pts.	Percent in Endoscopic Remission		
			0 to 3 mo.	0 to 6 mo.	0 to 12 mo.
#1	Lansoprazole 15 mg daily	86	90%*	87%*	84%*
	Placebo	83	49%	41%	39%
#2	Lansoprazole 30 mg daily	18	94%*	94%*	85%*
	Lansoprazole 15 mg daily	15	87%*	79%*	70%*
	Placebo	15	33%	0%	0%

%=Life Table Estimate  
\* (p < 0.001) versus placebo.

In trial #2, no significant difference was noted between lansoprazole 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 4 and 8 weeks was significantly higher with lansoprazole 15 mg and 30 mg once a day than with placebo (Table 9). [See Indications and Usage (1.4).]

Week	Lansoprazole			Placebo (N = 64)
	15 mg daily (N = 65)	30 mg daily (N = 63)	60 mg daily (N = 61)	
4	64.6%*	58.1%*	53.3%*	37.5%
8	92.2%*	96.8%*	93.2%*	76.7%

\* (p < 0.05) versus placebo.

Patients treated with any lansoprazole 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 lansoprazole 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 lansoprazole 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 lansoprazole 30 mg daily and the active control on symptom relief (i.e., abdominal pain) (Table 10). [See Indications and Usage (1.5).]

Study #1			
	Lansoprazole 30 mg daily	Active Control <sup>2</sup>	
Week 4	60% (53/88) <sup>3</sup>	28% (23/83)	
Week 8	79% (62/79) <sup>3</sup>	55% (41/74)	
Study #2			
	Lansoprazole 30 mg daily	Active Control <sup>2</sup>	
Week 4	53% (40/75)	38% (31/82)	
Week 8	77% (47/61) <sup>3</sup>	50% (33/66)	

<sup>1</sup> Actual observed ulcer(s) healed at time points + 2 days

<sup>2</sup> Dose for healing of gastric ulcer

<sup>3</sup> (p < 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 mg or 30 mg of lansoprazole 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 lansoprazole demonstrated no additional benefit in risk reduction of the NSAID-associated gastric ulcer than the 15 mg dose (Table 11). [See Indications and Usage (1.6).]

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

<sup>1</sup> % = Life Table Estimate

(p < 0.001) Lansoprazole 15 mg daily versus placebo; lansoprazole 30 mg daily versus placebo; and misoprostol 200 mcg q.i.d. versus placebo.

(p < 0.05) Misoprostol 200 mcg q.i.d. versus lansoprazole 15 mg daily; and misoprostol 200 mcg q.i.d. versus lansoprazole 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 12 and in Figures 1 and 2:

Variable	Placebo (n = 43)	Lansoprazole 15 mg (n = 80)	Lansoprazole 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

**Mean Severity of Day Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)**

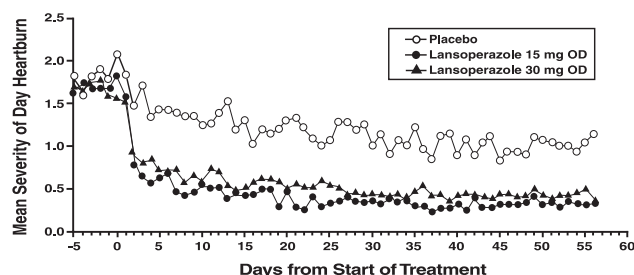
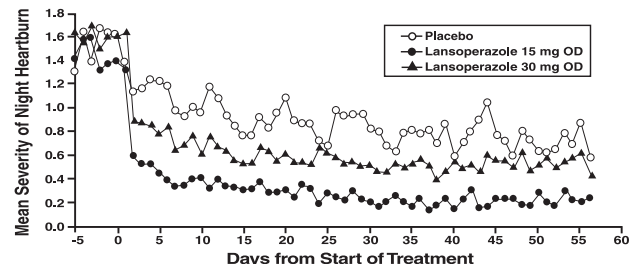


Figure 2

**Mean Severity of Night Heartburn By Study Day For Evaluable Patients (3=Severe, 2=Moderate, 1=Mild, 0=None)**



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 13:

Week	Lansoprazole			Placebo (N = 63)
	15 mg daily (N = 69)	30 mg daily (N = 65)	60 mg daily (N = 72)	
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 < 0.001) versus placebo.

† (p < 0.05) versus lansoprazole 15 mg.

In this study, all lansoprazole 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.

Lansoprazole was also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflux esophagitis. Lansoprazole at a dose of 30 mg was significantly more effective than ranitidine 150 mg twice daily as shown below (Table 14).

Week	Lansoprazole 30 mg daily (N = 115)	Ranitidine 150 mg twice daily (N = 127)
2	66.7%*	38.7%
4	82.5%*	52%
6	93%*	67.8%
8	92.1%*	69.9%

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

In addition, patients treated with lansoprazole 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 lansoprazole 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, lansoprazole produced healing rates similar to those shown above.

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of lansoprazole 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<sub>2</sub>-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. Lansoprazole 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<sub>2</sub>-receptor antagonists with lansoprazole, as all patients had demonstrated unresponsiveness to the histamine H<sub>2</sub>-receptor antagonist mode of treatment. It does indicate, however, that lansoprazole may be useful in patients failing on a histamine H<sub>2</sub>-receptor antagonist (Table 15). [See *Indications and Usage* (1.7).]

Week	Lansoprazole 30 mg daily (N = 100)	Ranitidine 150 mg twice daily (N = 51)
4	74.7%*	42.6%
8	83.7%*	32%

\* ( $p \leq 0.001$ ) 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 lansoprazole than in patients treated with placebo over a 12-month period (Table 16).

Trial	Drug	No. of Pts.	Percent in Endoscopic Remission		
			0 to 3 mo.	0 to 6 mo.	0 to 12 mo.
#1	Lansoprazole 15 mg daily	59	83%*	81%*	79%*
	Lansoprazole 30 mg daily	56	93%*	93%*	90%*
	Placebo	55	31%	27%	24%
#2	Lansoprazole 15 mg daily	50	74%*	72%*	67%*
	Lansoprazole 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, lansoprazole 15 mg and 30 mg were similar in maintaining remission.

In a U.S., randomized, double-blind, study, lansoprazole 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 lansoprazole 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, lansoprazole was significantly more effective than ranitidine in providing complete relief of both daytime and nighttime heartburn. Patients treated with lansoprazole 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, lansoprazole 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).] Lansoprazole was well tolerated at these high dose levels for prolonged periods (greater than 4 years in some patients). In most ZES patients, serum gastrin levels were not modified by lansoprazole. 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.

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

Lansoprazole Delayed-release Capsules, USP are available containing 15 mg or 30 mg of lansoprazole, USP.

The 15 mg capsules are white to off-white colored pellets filled in a hard gelatin capsule with green opaque cap and green opaque body, axially printed with **MYLAN** over **8015** in black ink on both cap and the body. They are available as follows:

NDC 0378-8015-93  
bottles of 30 capsules  
NDC 0378-8015-01  
bottles of 100 capsules  
NDC 0378-8015-10  
bottles of 1000 capsules

The 30 mg capsules are white to off-white colored pellets filled in a hard gelatin capsule with pink opaque cap and pink opaque body, axially printed with **MYLAN** over **8030** in black ink on both cap and the body. They are available as follows:

NDC 0378-8030-77  
bottles of 90 capsules  
NDC 0378-8030-05  
bottles of 500 capsules

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

#### 17 PATIENT COUNSELING INFORMATION

Patient should be informed of the following:

##### 17.1 Information for Patients

Lansoprazole is available as a capsule in 15 mg and 30 mg strengths. [See *Dosage and Administration* (2.3).]

- Lansoprazole should be taken before eating.
- Lansoprazole products SHOULD NOT BE CRUSHED OR CHEWED.

##### Administration Options

Lansoprazole Delayed-release Capsules

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

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Manufactured in India by:

**Matrix Laboratories Limited**

Secunderabad — 500 003, India

Code No. MH/DRUGS/25/NKD/89

Manufactured for:



**MYLAN®**

**Mylan Pharmaceuticals Inc.**

Morgantown, WV 26505 U.S.A.

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