PRODUCT MONOGRAPH

^{Pr}LANSOPRAZOLE

Lansoprazole

Delayed-Release Capsules USP

30 mg

H^+, K^+ – ATPase Inhibitor

DOMINION PHARMACAL
6111 Royalmount Ave., Suite 100
Montréal, Québec
H4P 2T4

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Lansoprazole Delayed-Release Capsules, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Delayed-release capsules/30 mg	None. For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

INDICATIONS AND CLINICAL USE

Adults
LANSOPRAZOLE (lansoprazole delayed-release capsules) is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

1. Reflux esophagitis including patients with Barrett's esophagus, and patients poorly responsive to an adequate course of therapy with histamine H_2-receptor antagonists.
2. Symptomatic Gastroesophageal reflux disease (sGERD); treatment of heartburn and other symptoms associated with GERD.
3. Pathological hypersecretory conditions including Zollinger-Ellison Syndrome (see DOSAGE AND ADMINISTRATION).

Pediatric GERD (erosive and non-erosive esophagitis) (1 to 17 years of age):
LANSOPRAZOLE is indicated for treatment of erosive and non-erosive GERD in children, aged 1 to 17 years. The clinical trial treatment period did not extend beyond 12 weeks.

CONTRAINDICATIONS

- Patients with known hypersensitivity to any component of the formulations. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

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

Decreased gastric acidity due to any means, including proton pump inhibitors (PPIs), increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections.

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate (see DRUG INTERACTIONS).

Bone Fracture
Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiply daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Carcinogenesis and Mutagenesis
Safety concerns of long-term treatment relate to hypergastrinemia, possible enterochromaffin-like (ECL) effect and carcinoid formation. ECL cell hyperplasia and gastric carcinoid tumours were observed in four animal studies.

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day about 1 to 40 times the exposure on a body surface (mg/m^2) basis, of a 50 kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). Lansoprazole produced dose-related gastric entero-chromaffin-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 body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rats. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. Lansoprazole also induced a low, non-dose-related incidence of carcinoid tumours in the gastric

mucosa in several dose groups (one female mouse in the 15 mg/kg/day group, one male mouse in the 150 mg/kg/day group, and 2 males and 1 female in the 300 mg/kg/day group). It also produced an increased incidence of liver tumours (hepatocellular adenoma plus carcinoma). The tumour incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) 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 body surface area).

Analysis of gastric biopsy specimens from patients after short-term treatment of proton pump inhibitors have not detected ECL cell effects similar to those seen in animal studies. Longer term studies in humans revealed a slight increase in the mean ECL-cell density, although there was no microscopic evidence of cell hyperplasia. Similar results were seen in the maintenance treatment studies, where patients received up to 15 months of lansoprazole therapy. Serum gastrin values increased significantly from their baseline values but reached a plateau after two months of therapy. By one month post-treatment, fasting serum gastrin values returned to lansoprazole therapy baseline. Moreover, results from gastric biopsies from short-term, long-term and maintenance treatment studies indicate that there are no clinically meaningful effects on gastric mucosa morphology among lansoprazole-treated patients. For further details, see information under PHARMACOLOGY and TOXICOLOGY.

Endocrine and Metabolism

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically (see ADVERSE REACTIONS).

The chronic use of PPIs may lead to hypomagnesemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

Genitourinary

In the 24-month toxicology study in rats, after 18 months of treatment, Leydig cell hyperplasia increased above the concurrent and historical control level at dosages of 15 mg/kg/day or higher.

Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one-year toxicity study.

These changes are associated with endocrine alterations which have not been, to date, observed in humans. For further details, see information under PHARMACOLOGY and TOXICOLOGY.

Hepatic/Biliary/Pancreatic

Use in Patients with Hepatic Impairment

It is recommended that the initial dosing regimen need not be altered for patients with mild or moderate liver disease, but for patients with moderate impairment, doses higher than 30 mg per day should not be administered unless there are compelling clinical indications. Dose reduction in patients with severe hepatic disease should be considered.

Ophthalmologic

Retinal atrophy

In animal studies, retinal atrophy was observed in rats dosed orally for 2 years with lansoprazole at doses of 15 mg/kg/day and above. These changes in rats are believed to be associated with the effects of taurine imbalance and phototoxicity in a susceptible animal model.

Clinical data available from long-term lansoprazole delayed-release capsules studies are not suggestive of any drug-induced eye toxicity in humans. In humans, there are presently no concerns for ocular safety with short-term lansoprazole treatment and the risks associated with long-term use for nearly five years appear to be negligible.

The finding of drug-induced retinal atrophy in the albino rat is considered to be species-specific with little relevance for humans. For further details, see information under PHARMACOLOGY and TOXICOLOGY.

Renal

No dosage modification of lansoprazole is required in patients with renal insufficiency.

Use in Women

Over 4000 women were treated with lansoprazole. The incidence rates of adverse events are similar to those seen in males.

Special Populations

Pregnant Women: Reproductive studies conducted in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area), and in rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area), did not disclose any evidence of a teratogenic effect. Maternal toxicity and a significant increase in fetal mortality were observed in the rabbit study at doses above 10 mg/kg/day. In rats, maternal toxicity and a slight reduction in litter survival and weights were noted at doses above 100 mg/kg/day.

There are no adequate or well-controlled studies in pregnant women. Therefore, lansoprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because drugs are excreted in human milk, lansoprazole should not be given to nursing mothers unless its use is considered essential.

Pediatrics (1 to 17 years of age): Safety and effectiveness have been established in pediatric patients 1 year to 17 years for short-term up to 12 weeks of symptomatic GERD and erosive esophagitis. Use of lansoprazole in this population is supported by evidence of adequate and well controlled studies of lansoprazole in adults with additional clinical, pharmacokinetic, pharmacodynamic, and safety studies performed in pediatric patients. The adverse events (AEs) profile in pediatric patients is similar to that of adults. There were no adverse events reported in U.S. clinical studies that were not previously observed in adults. Dose safety and effectiveness have not been established in patients <1 year.

Geriatrics: Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category (> 71 years of age) may already be at high risk for osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

The incidence rates of adverse events and laboratory test abnormalities are similar to those seen in other age groups. The initial dosing regimen need not be altered for elderly patients, but subsequent doses higher than 30 mg per day should not be administered unless additional gastric acid suppression is necessary.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Since 1991, lansoprazole has been approved in over 100 countries around the world, and about 250 million patients have been treated. Worldwide, over 10,000 patients have been treated with lansoprazole during Phase II-III short-term and long-term clinical trials involving various dosages and duration of treatment. In general, lansoprazole treatment has been well tolerated.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Lansoprazole delayed-release capsules

Short-Term Studies

The following adverse events were reported to have a possible or probable relationship to drug as described by the treating physician in 1% or more of lansoprazole delayed-release capsules-treated patients who participated in placebo- and positive-controlled trials (Table 1 and Table 2, respectively). Numbers in parentheses indicate the percentage of the adverse events reported.

Table 1 Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies in Takeda† Safety Database		
Body System/ Adverse Event*	**Lansoprazole@ (N=817), N (%)**	**Placebo (N=254), N (%)**
Body as a Whole		
Headache	63 (7.7)	31 (12.2)
Abdominal Pain	19 (2.3)	3 (1.2)
Digestive System		
Diarrhea	29 (3.5)	6 (2.4)
Nausea	9 (1.1)	5 (2.0)
Vomiting	7 (0.9)	3 (1.2)
Liver Function Tests Abnormal	2 (0.2)	3 (1.2)
Nervous System		
Dizziness	8 (1.0)	2 (0.8)
† Takeda Pharmaceuticals America, Inc. * Events reported by at least 1% of patients on either treatment are included. @ Doses 15 mg, 30 mg and 60 mg q.d. for 4-8 weeks.		

In the Takeda Safety Database, all short-term, Phase II/III studies, one or more treatment-emergent AEs were reported by 715/1359 (52.6%) lansoprazole-treated patients; of those considered to be possibly or probably treatment-related AEs, one or more were reported by 276/1359 (20.3%) lansoprazole-treated patients. In all short-term, Phase II/III studies, one or more treatment-emergent AEs were reported by 150/254 (59.1%) placebo-treated patients; of those considered to be possibly or probably treatment-related AEs, one or more were reported by 56/254 (22.0%).

The most frequent AEs reported in the European short-term studies were diarrhea (3.3%), laboratory test abnormal (2.3%), headache (1.5%), constipation (1.2%), asthenia (1.1%), dizziness (1.1%), and abdominal pain (1.0%). The most frequent AEs reported in the Asian short-term studies were unspecified laboratory test abnormalities (7.3%), eosinophilia (1.0%), and increased SGPT (1.0%).

Table 2 Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Positive-Controlled Studies in Takeda Safety Database		
Body System/ Adverse Event*	**Lansoprazole@ (N=647), N (%)**	**Ranitidine (N=393), N (%)**
Body as a Whole		
Headache	26 (4.0)	14 (3.6)
Abdominal Pain	8 (1.2)	3 (0.8)
Digestive System		
Diarrhea	27 (4.2)	8 (2.0)
Nausea	7 (1.1)	4 (1.0)
Nervous System		
Dizziness	8 (1.2)	3 (0.8)
Skin and Appendages		
Rash	7 (1.1)	1 (0.3)
* Events reported by at least 1% of patients on either treatment are included.		

[@] Doses 15 mg, 30 mg and 60 mg q.d. for 4-8 weeks.

Gastroesophageal Reflux Disease (GERD) Studies

U.S. Placebo-Controlled Studies

All adverse events considered possibly/probably treatment-related with an incidence of at least 5% in any treatment group are displayed by COSTART body system and term and by treatment group in Table 3.

Table 3
Adverse Events Possibly/Probably Related to Treatment, Reported by ≥ 5% of Patients in the U.S. Placebo-Controlled Non-Erosive GERD Studies

	Placebo	Lansoprazole[@]
Body System/ COSTART term	**N=71** **% (n)**	**N=249** **% (n)**
Total patients		
Any event	16.9 (12)	28.5 (71)*
Body as a Whole		
Abdominal Pain	1.4 (1)	6.0 (15)
Headache	7.0 (5)	7.6 (19)
Digestive System		
Diarrhea	2.8 (2)	5.2 (13)

* Statistically significantly different versus placebo at p = 0.05 level.
[@] Doses 15 mg and 30 mg q.d. for 8 weeks.

The most commonly reported (incidence ≥ 5% in any treatment group) treatment-emergent adverse events for lansoprazole patients were headache (14.9%), pharyngitis (9.6%), abdominal pain (8.8%), diarrhea (7.6%) and rhinitis (6.4%) and for placebo patients were headache (9.9%) and pharyngitis (9.9%). There were no clinically or statistically significant differences between lansoprazole and placebo when evaluated for treatment-emergent adverse events.

U.S. Positive-Controlled Studies

All possibly/probably treatment-related adverse events with an incidence of at least 5% in either treatments are displayed by body system, COSTART term, and treatment in Table 4.

Table 4
Most Frequently[a] Reported Possibly/Probably Treatment-Related Adverse Events by Treatment in the Positive-Controlled Non-Erosive GERD Studies

	Treatment % (n)	
Body System/COSTART term	**RAN** (N=283)	**LAN[@]** (N=572)
Any event	17 (49)	16 (91)
Body as a Whole		
Abdominal Pain	2 (5)	5 (29) *
Digestive System		
Diarrhea	6 (18)	4 (23)

RAN = ranitidine 150 mg b.i.d.; LAN = lansoprazole 15 mg and 30 mg q.d.
[a] Reported by ≥ 5% of patients in any treatment.
* Statistically significantly different versus ranitidine at p = 0.05 level.
[@] Doses 15 mg and 30 mg q.d. for 8 weeks.

The most frequently reported (≥ 5% of patients in any treatment) treatment-emergent adverse events for lansoprazole-treated patients were abdominal pain (9%), diarrhea (7%), and headache (6%) and for ranitidine-treated patients were diarrhea (9%), abdominal pain (7%), and headache (7%). There were no clinically or statistically significant differences between lansoprazole- and ranitidine-treated patients in the percentage of patients reporting specific treatment-emergent adverse events.

Maintenance Studies

U.S. Studies

Treatment-emergent AEs with an incidence of at least 2% in any treatment group of the maintenance treatment studies occurring from the start of maintenance treatment to the first recurrence of disease are displayed by body system and COSTART term, and by treatment group in Table 5.

There were no frequently reported (≥ 2.0%, incidence) severe AEs in the treatment-emergent or the possibly/probably treatment-related event categories with onset at any point from the start of maintenance treatment to the time of first recurrence of disease.

Table 5
Treatment-Emergent AEs Reported by ≥ 2% of the Placebo and Lansoprazole Patients to the Time of First Recurrence of Disease[@] in the Maintenance Treatment Studies

Treatment Group	Placebo	Lansoprazole
	CUM*	**CUM***
	N=236	**N=386**
Mean Exposure (Days)	**105.4**	**267.5**
Body System/COSTART term	% (n)	% (n)
Total patients		
Any event	39.4 (93)	70.5 (272)
Body as a Whole		
Abdominal pain	3.0 (7)	5.2 (20)
Accidental injury	2.1 (5)	5.4 (21)
Back pain	4.2 (10)	3.1 (12)
Chest pain	0.8 (2)	2.3 (9)
Flu syndrome	3.8 (9)	7.3 (28)
Headache	6.4 (15)	11.4 (44)
Infection	1.3 (3)	2.1 (8)
Pain	0.8 (2)	2.6 (10)
Digestive System		
Diarrhea	5.5 (13)	9.8 (38)
Gastrointestinal anomaly (polyp)	0.8 (2)	4.4 (17)
Nausea	1.3 (3)	2.8 (11)
Tooth disorder	0.4 (1)	2.1 (8)
Vomiting	0.4 (1)	3.4 (13)
Musculoskeletal System		
Arthralgia	1.3 (3)	4.4 (17)
Myalgia	1.3 (3)	2.1 (8)

Table 5 Treatment-Emergent AEs Reported by ≥ 2% of the Placebo and Lansoprazole Patients to the Time of First Recurrence of Disease[@] in the Maintenance Treatment Studies		
Treatment Group	**Placebo**	**Lansoprazole**
Nervous System		
Dizziness	0.4 (1)	2.8 (11)
Respiratory System		
Bronchitis	1.3 (3)	3.1 (12)
Cough increased	0	2.3 (9)
Pharyngitis	9.3 (22)	17.1 (66)
Rhinitis	1.3 (3)	5.7 (22)
Sinusitis	2.5 (6)	6.5 (25)
Skin and Appendages		
Rash	3.0 (7)	4.7 (18)
Urogenital System		
Urinary tract infection	2.5 (6)	4.1 (16)
[@] Until time of first recurrence, withdrawal or end of maintenance treatment * CUM - Cumulative		

European Studies

The AEs reported by at least 2% of patients in any treatment group are displayed by COSTART body system and term and by treatment group for controlled long-term European Studies in Table 6.

Table 6 Treatment-Emergent AEs Reported by ≥ 2% of Patients Treated with H_2-RA's or Lansoprazole in Long-Term, Phase II/III H_2-RA Controlled European Studies		
Treatment Group	**Lansoprazole (N=263)**	**H_2-RAs (N=161)**
Body System/COSTART term	% (n)	% (n)
Total patients		
Any event	49.8 (131)	46.6 (75)
Body as a Whole		
Abdominal pain	3.0 (8)	3.7 (6)
Back pain	2.3 (6)	0.6 (1)
Accidental injury	1.5 (4)	2.5 (4)
Infection	1.1 (3)	3.1 (5)
Cardiovascular System		
Hypertension	1.9 (5)	2.5 (4)
Digestive System		
Diarrhea	9.1 (24)	4.3 (7)
Gastritis	5.3 (14)	1.2 (2)
Constipation	2.7 (7)	2.5 (4)
Vomiting	1.9 (5)	3.1 (5)
Dyspepsia	1.1 (3)	3.1 (5)
Musculoskeletal System		
Arthralgia	1.9 (5)	2.5 (4)
Nervous System		
Dizziness	1.9 (5)	2.5 (4)
Respiratory System		

Table 6 Treatment-Emergent AEs Reported by ≥ 2% of Patients Treated with H_2-RA's or Lansoprazole in Long-Term, Phase II/III H_2-RA Controlled European Studies		
Treatment Group	**Lansoprazole (N=263)**	**H_2-RAs (N=161)**
Respiratory Disorder	2.3 (6)	3.1 (5)
Cough increased	1.1 (3)	2.5 (4)

The AEs reported by at least 1% of patients receiving lead-in open-label lansoprazole treatment in long-term European Studies are diarrhea (5.7%), esophagitis (2.5%), abdominal pain (2.1%), gastritis (2.1%), flatulence (1.3%), headache (1.1%), constipation (1.0%), and nausea (1.0%). The incidence of AEs reported in the lead-in open-label period of the European studies was similar to that seen in controlled studies, however, the overall incidence was lower for the lead-in open- label studies than for the H_2-RA controlled studies (27.5% versus 49.8%, respectively).

Pediatrics

The adverse event profile in pediatric patients resembled that of adults taking lansoprazole. The most frequently reported (2 or more patients) treatment-related adverse events in patients 1 to 11 years of age (N=66) were constipation (5%) and headache (3%). There were no adverse events reported in this U.S. clinical study that were not previously observed in adults.

The most frequently reported (at least 3%) treatment-related adverse events in patients 12-17 years of age (N=87) were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported as occurring in <1% of adult patients, was reported in this study by 3 adolescent patients with nonerosive GERD, who had dizziness concurrently with other events (such as migraine, dyspnea, and vomiting).

In another study, an 8½-year-old female experienced moderate hot flashes and arterial hypertension after receiving lansoprazole 17.7 mg/m^2 for 5 days. However, blood pressure values were not recorded. The investigator considered the event possibly related to study drug. Study drug was discontinued and the symptoms resolved. This child experienced the same side effects at a later date when treated with ranitidine.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. (Other adverse reactions have been observed during post-marketing surveillance. Please also refer to Postmarketing Experience).

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

Cardiovascular System: Angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), tachycardia, vasodilation;

Digestive System: Abnormal stools, anorexia, bezoar, carcinoid, cardiospasm, cholelithiasis, colitis, constipation, dry mouth/thirst, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, oral monoliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, tongue disorder, ulcerative colitis, ulcerative stomatitis;

Endocrine System: Diabetes mellitus, goiter, hyperglycemia/hypoglycemia, hypothyroidism;

Hematologic and Lymphatic System*: Anemia, hemolysis, lymphadenopathy;

Metabolic and Nutritional Disorders: Gout, dehydration, peripheral edema, weight gain/loss;

Musculoskeletal System: Arthritis/arthralgia, 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, libido increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, syncope, thinking abnormality, tremor, vertigo;

Respiratory System: Asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pleural disorder, pneumonia, stridor, upper respiratory inflammation/infection;

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, ophthalmologic disorders, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect;

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

* The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear.

Abnormal Hematologic and Clinical Chemistry Findings

In addition, the following changes in laboratory parameters were reported as adverse events. Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased

creatinine, increased alkaline phosphatase, increased gamma globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. 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) placebo patients and 0.4% (11/2677) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

Post-Market Adverse Drug Reactions

These events were reported during postmarketing surveillance. Estimates of frequency cannot be made since such events are reported voluntarily from a population of unknown size. Due to the uncontrolled nature of spontaneous reports, a clear causal relationship to lansoprazole cannot be established.

Body as a Whole - hypersensitivity reactions, including anaphylaxis; Digestive System - colitis, hepatotoxicity, pancreatitis, vomiting; Hematologic and Lymphatic System - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; Metabolism and Nutritional Disorders - hypomagnesemia; Musculoskeletal System - myositis, osteoporosis and osteoporosis-related fractures; Skin and Appendages - severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); Special Senses - speech disorder; Urogenital System – urinary retention, interstitial nephritis.

In an estimated exposure of 240 million patients worldwide (in both postmarketing surveillance and the clinical trials), the most commonly reported ophthalmic adverse events are amblyopia (13) and vision blurred (67) according to the MedDRA terminology. All the 13 cases of amblyopia had the reported term/verbatim "blurred or smeary vision". Only two of these 13 reports were considered serious, and both are foreign-sourced reports with very little information provided. Among the 67 reports with the "vision blurred," 10 were considered serious and might be related to optic neuritis/neuropathy, whether or not believed related to the drug. In two of these ten cases, one of the examining ophthalmologists proposed a diagnosis of AION. Eight out of the ten cases were foreign-sourced. Only two US-sourced serious cases involved the report of blurred vision. Both were consumer reports without any detailed information. No physician assessed any causality in either case.

Withdrawal of long term PPI therapy can lead to aggravation of acid related symptoms and may result in Rebound Acid Hyper-secretion.

DRUG INTERACTIONS

Overview

Lansoprazole is metabolized through the cytochrome P450 system, specifically through CYP3A and CYP2C19. 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, acetylsalicylic acid, ibuprofen, phenytoin, prednisone, antacids, diazepam, clarithromycin, propranolol, amoxicillin or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

Lansoprazole causes a profound and long lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Drug-Drug Interactions

Theophylline

When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen, which is unlikely to be of clinical concern. Nonetheless, individual patients may require adjustment of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Sucralfate

In a single-dose crossover study when 30 mg of lansoprazole was administered concomitantly with one gram of sucralfate in healthy volunteers, absorption of lansoprazole was delayed and its bioavailability was reduced. The value of lansoprazole AUC was reduced by 17% and that for C_{max} was reduced by 21%.

In a similar study when 30 mg of lansoprazole was administered concomitantly with 2 grams of sucralfate, lansoprazole AUC and C_{max} were reduced by 32% and 55%, respectively. When lansoprazole dosing occurred 30 minutes prior to sucralfate administration, C_{max} was reduced by only 28% and there was no statistically significant difference in lansoprazole AUC. Therefore, lansoprazole may be given concomitantly with antacids but should be administered at least 30 minutes prior to sucralfate.

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 should not be co-administered with atazanavir. This appears to be a class effect. It is theoretically possible that lansoprazole may also interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Methotrexate
Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of high dose methotrexate with PPIs have been conducted. 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 methrotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse reactions were noted. However, this study was conducted with low doses of methotrexate. A drug interaction study with high doses of methotrexate has not been conducted.

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.

Drug-Food Interactions
Food reduces the peak concentration and the extent of absorption by about 50% to 70%. Therefore, it is recommended that lansoprazole delayed-release capsules be administered in the morning prior to breakfast.

Drug-Laboratory Interactions
During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference lansoprazole treatment should be temporarily stopped before CgA measurements.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
LANSOPRAZOLE should be taken daily before breakfast. Where the product may be used twice daily, it should be taken prior to breakfast and another meal. LANSOPRAZOLE capsules SHOULD NOT BE CRUSHED OR CHEWED. Capsules should be swallowed whole.

Reflux Esophagitis or Poorly Responsive Reflux Esophagitis Including Patients with Barrett's Esophagus
The recommended adult oral dose is 30 mg daily before breakfast for four to eight weeks (see INDICATIONS AND CLINICAL USE).

Maintenance Treatment of Healed Reflux Esophagitis
For the long-term management of patients with healed reflux esophagitis, 15 mg lansoprazole given once daily before breakfast has been found to be effective in controlled clinical trials of 12 months' duration (see information under CLINICAL TRIALS).

The recommended adult oral dose of lansoprazole for maintenance treatment of patients with healed reflux esophagitis is 15 mg daily before breakfast (see INDICATIONS AND CLINICAL USE).

Treatment and Maintenance of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of lansoprazole in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg b.i.d. have been administered. Daily dosages 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 four years (see information under CLINICAL TRIALS).

Gastroesophageal Reflux Disease (GERD)
Short-Term Treatment of Symptomatic GERD
The recommended adult oral dose for the treatment of heartburn and other symptoms associated with GERD is 15 mg daily before breakfast for up to 8 weeks. If significant symptom relief is not obtained within 4 to 8 weeks, further investigation is recommended.

Pediatric GERD (erosive and non-erosive esophagitis)
Children 1 to 11 years of age
The recommended pediatric oral dose for children 1 to 11 years of age is 15 mg (≤ 30 kg) and 30 mg (>30 kg) once daily for up to 12 weeks. An increase in dose may be beneficial in some children (see CLINICAL TRIALS).

Children 12 to 17 years of age
For adolescents of 12 to 17 years, the same approved regimen for adults can be used.

Patients with Hepatic Impairment
The daily dose of lansoprazole should not exceed 30 mg (see WARNINGS AND PRECAUTIONS).

Patients with Renal Impairment
No dosage modification of lansoprazole is necessary (see WARNINGS AND PRECAUTIONS).

Elderly Patients
The daily dose should not exceed 30 mg (see WARNINGS AND PRECAUTIONS).

Missed Dose
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose.

Administration
LANSOPRAZOLE should be taken daily before breakfast. Where the product may be used twice daily, it should be taken prior to breakfast and another meal. LANSOPRAZOLE capsules SHOULD NOT BE CRUSHED OR CHEWED. Capsules should be swallowed whole.

Concomitant Antacid Use
Simultaneous administration of lansoprazole with aluminum and magnesium hydroxide or magaldrate results in lower peak plasma levels, but does not significantly reduce bioavailability. Antacids may be used concomitantly if required. If sucralfate is to be given concomitantly, lansoprazole should be administered at least 30 minutes prior to sucralfate (see ACTIONS AND CLINICAL PHARMACOLOGY; Absorption with Antacids). In clinical trials, antacids were administered concomitantly with lansoprazole delayed-release capsules; this did not interfere with its effect.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored. Lansoprazole is not removed from the circulation by hemodialysis. In one reported case of overdose, the patient consumed 600 mg of lansoprazole with no adverse reaction.

Oral doses up to 5000 mg/kg in rats (approximately 1300 times the recommended human dose based on body surface area) and mice (about 675.7 times the recommended human dose based on body surface area) did not produce deaths or any clinical signs.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Lansoprazole delayed-release capsules inhibit the gastric H^+, K^+-ATPase (the proton pump) which catalyzes the exchange of H^+ and K^+. They are effective in the inhibition of both basal acid secretion and stimulated acid secretion.

Pharmacodynamics
In healthy subjects, single and multiple doses of lansoprazole delayed-release capsules (15 mg to 60 mg) have been shown to decrease significantly basal gastric acid output and to increase

significantly mean gastric pH and percent of time at pH >3 and 4. These doses have also been shown to reduce significantly meal-stimulated gastric acid output and gastric secretion volume. Single or multiple doses of lansoprazole delayed-release capsules (10 mg to 60 mg) reduced pentagastrin-stimulated acid output. In addition, lansoprazole delayed-release capsules have been demonstrated to reduce significantly basal and pentagastrin-stimulated gastric acid secretion in hypersecretory patients.

A dose-response effect was analyzed by considering the results from clinical pharmacology studies that evaluated more than one dose of lansoprazole delayed-release capsules. The results indicated that, in general, as the dose was increased from 7.5 mg to 30 mg, there was a decrease in mean gastric acid secretion and an increase in the average time spent at higher pH values (pH >4).

The results of pharmacodynamic studies with lansoprazole delayed-release capsules in normal subjects suggest that doses of 7.5 to 10 mg are substantially less effective in inhibiting gastric acid secretion than doses of 15 mg or greater. In view of these results, the doses of lansoprazole delayed-release capsules evaluated in the principal clinical trials ranged from 15 mg to 60 mg daily.

Pharmacokinetics

Lansoprazole delayed-release capsules contain an enteric-coated granule formulation of lansoprazole to ensure that absorption of lansoprazole begins only after the granules leave the stomach (lansoprazole is acid-labile). Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15 mg to 60 mg after single-oral administration. Lansoprazole pharmacokinetics are unaltered by multiple dosing and the drug does not accumulate.

Lansoprazole delayed-release capsules are highly bioavailable when administered orally. In a definitive absolute bioavailability study, the absolute bioavailability was shown to be 86% for a 15 mg capsule and 80% for a 30-mg capsule. First pass effect is apparently minimal.

Table 9 summarizes the pharmacokinetic parameters (T_{max}, $T_{½}$, AUC and C_{max}) of lansoprazole delayed-release capsules in healthy subjects. For a summary of pharmacokinetic, metabolism and excretion data in animals, see PHARMACOLOGY.

Table 9
Pharmacokinetic Parameters of Lansoprazole Delayed-Release Capsules Pooled Across Phase I Studies

Parameter	T_{max} (h)	$T_{½}$ (h)	AUC[#] (ng•h/mL)	C_{max}[#] (ng/mL)
Mean	1.68	1.53	2133	824
Median	1.50	1.24	1644	770
SD	0.80	1.01	1797	419
% CV	47.71	65.92	84.28	50.81
Min	0.50	0.39	213	27
Max	6.00	8.50	14203	2440
N[@]	345	285	513	515

[#] Normalized to a 30 mg dose
[@] Number of dosages associated with a parameter

Absorption: The absorption of lansoprazole is rapid, with mean peak plasma levels of lansoprazole occurring at approximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) are approximately proportional to dose throughout the range that has been studied (up to 60 mg).

Absorption with Food

Food reduces the peak concentration and the extent of absorption by about 50% to 70%. Moreover, the results of a pharmacokinetic study that compared the bioavailability of lansoprazole following a.m. dosing (fasting) versus p.m. dosing (three hours after a meal) indicated that both C_{max} and AUC values were increased by approximately two-fold or more with a.m. dosing. Therefore, it is recommended that lansoprazole delayed-release capsules be administered in the morning prior to breakfast.

Absorption with Antacids

Simultaneous administration of lansoprazole delayed-release capsules with aluminum and magnesium hydroxide or magaldrate resulted in lower peak serum levels, but did not significantly reduce the bioavailability of lansoprazole.

In a single-dose crossover study when 30 mg of lansoprazole was administered concomitantly with one gram of sucralfate in healthy volunteers, absorption of lansoprazole was delayed and its bioavailability was reduced. The value of lansoprazole AUC was reduced by 17% and that for C_{max} was reduced by 21%.

In a similar study when 30 mg of lansoprazole was administered concomitantly with 2 grams of sucralfate, lansoprazole AUC and C_{max} were reduced by 32% and 55%, respectively. When lansoprazole dosing occurred 30 minutes prior to sucralfate administration, C_{max} was reduced by only 28% and there was no statistically significant difference in lansoprazole AUC. Therefore, lansoprazole may be given concomitantly with antacids but should be administered at least 30 minutes prior to sucralfate.

Distribution: The apparent volume of distribution of lansoprazole is approximately 15.7 (± 1.9) L, distributing mainly in extracellular fluid. Lansoprazole is 97% bound to plasma proteins. The mean total body clearance (CL) of lansoprazole was calculated at 31 ± 8 L/h, and the volume of distribution (V_{ss}) was calculated to be 29 (± 4) L.

Metabolism: Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma; the hydroxylated sulfinyl and the sulfone derivatives of lansoprazole. These metabolites have very little or no antisecretory activity. Within the parietal cell canaliculus, lansoprazole is thought to be transformed into two active metabolites that inhibit acid secretion by H^+, K^+-ATPase, but these metabolites are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect the duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours while the acid inhibitory effect lasts over 24 hours.

Excretion: Following single dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. After a 30 mg single oral dose of ^{14}C-lansoprazole,

approximately one-third of the dose was excreted in the urine and approximately two-thirds were recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of lansoprazole were studied in pediatric patients with Gastroesophageal Reflux Disease (GERD) aged 1 to 11 years, with lansoprazole doses of 15 mg q.d. for subjects weighing ≤30 kg and 30 mg q.d. for subjects weighing >30 kg. The pharmacokinetics were also studied in adolescents aged 12-17 years with GERD following 15 mg or 30 mg q.d. of lansoprazole.

Pharmacokinetic parameters for lansoprazole following 15 or 30 mg q.d. doses of lansoprazole to children aged 1 to 11 years and adolescents aged 12 to 17 years, as well as those observed from healthy adult subjects, are summarized in Table 10.

Table 10
Mean ± SD Pharmacokinetic Parameters of Lansoprazole in Children, Adolescents and Adults

Pharmacokinetic Parameter	Children Aged 1 to 11 yrs (M97-808)		Adolescents Aged 12 to 17 yrs (M97-640)		Healthy Adults Aged ≥18 yrs
	15 mg [a]	30 mg [a]	15 mg	30 mg	30 mg [b]
T_{max}(h)	1.5 ± 0.7	1.7 ± 0.7	1.6 ± 0.7	1.7 ± 0.7	1.7 ± 0.8
C_{max} (ng/mL)	790.9 ± 435.4	898.5 ± 437.7	414.8 ± 215.5	1005 ± 604.9	824 ± 419
C_{max}/D(ng/mL/mg)	-	-	27.7 ± 14.4	33.5 ± 20.2	27.5 ± 14.0
AUC (ng•h/mL)	1707 ± 1689	1883 ± 1159	1017 ± 1737	2490 ± 2522	2133 ± 1797
AUC/D (ng•h/mL/mg)	-	-	67.8 ± 115.8	83.0 ± 84.1	71.1 ± 59.9
$t_{1/2}$ (h) [c]	0.68 ± 0.21	0.71 ± 0.22	0.84 ± 0.26	0.95 ± 0.31	1.19 ± 0.52

[a] Subjects with a body weight of ≤30 kg were administered a 15-mg dose; subjects with a body weight of >30 kg were administered a 30-mg dose.
[b] Data obtained from healthy adult subjects normalized to a 30-mg dose.
[c] Harmonic mean ± Pseudo Standard Deviation.

In general, the pharmacokinetics of lansoprazole in children and adolescents (aged 1 to 17 years) with GERD were similar to those observed in healthy adult subjects.

Children 1 to 11 years old weighing ≤ 30 kg received a 15 mg dose and children weighing >30 kg received a 30 mg dose. When normalized for body weight, the mean lansoprazole dose was similar for the two dosing groups (0.82 mg/kg for 15 mg dose group and 0.74 mg/kg for 30 mg dose group). The C_{max} and AUC values were therefore similar for both the 15 mg and 30 mg dose groups.

In adolescent subjects aged 12 to 17 years, a nearly proportional increase in plasma exposure was observed between 15 mg and 30 mg q.d. dosing groups. Plasma exposure of lansoprazole was not affected by body weight or age; and nearly dose-proportional increases in plasma exposure were observed between the two dose groups in the study. The results of the study in adolescents demonstrated that the pharmacokinetics of lansoprazole in this group is similar to that previously reported in healthy adult subjects.

Geriatrics: The results from the studies that evaluated the pharmacokinetics of lansoprazole following oral administration in an older population revealed that in comparison with younger subjects, older subjects exhibited significantly larger AUCs and longer $t_{½}$s. Lansoprazole did not accumulate in the older subjects upon multiple dosing since the longest mean $t_{½}$ in the studies was 2.9 hours, and lansoprazole is dosed once daily. C_{max} in the elderly was comparable to that found in adult subjects.

Gender: The pharmacokinetic data of intravenous lansoprazole in females is limited; however, in a study with oral lansoprazole comparing 12 male and 6 female subjects, no gender differences were found in pharmacokinetics or intragastric pH results (see PRECAUTIONS; Use in Women).

Race: The pooled pharmacokinetic parameters of oral administered lansoprazole from twelve U.S. Phase I studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects are approximately twice that seen in pooled U.S. data, however, the inter-individual variability is high. The C_{max} values are comparable.

Hepatic Insufficiency: As would be expected with a drug that is primarily metabolized by the liver, in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) chronic hepatic disease, the plasma half-life of the drug after oral administration increased to 5.2 hours compared to the 1.5 hours half-life in healthy subjects. An increase in AUC of 3.4 fold was observed in patients with hepatic impairment versus healthy subjects (7096 versus 2645 ng•h/mL) which was due to slower elimination of lansoprazole; however, C_{max} was not significantly affected. Dose reduction in patients with severe hepatic disease should be considered.

Renal Insufficiency: In patients with mild (Cl_{cr} 40 to 80 mL/min), moderate (Cl_{cr} 20 to 40 mL/min) and severe (Cl_{cr} <20 mL/min) chronic renal impairment, the disposition of lansoprazole after oral administration was very similar to that of healthy volunteers.

The impact of dialysis on lansoprazole was evaluated from a pharmacokinetic standpoint, and there were no significant differences in AUC, C_{max} or $t_{½}$ between dialysis day and dialysis-free day. Dialysate contained no measurable lansoprazole or metabolite. Lansoprazole is not significantly dialysed.

STORAGE AND STABILITY

LANSOPRAZOLE delayed-release capsules should be stored between 15 ºC and 30ºC. Protect from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:
LANSOPRAZOLE is supplied in delayed-release capsules for oral administration. The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in one dosage strength: 30 mg of lansoprazole per capsule.

Non-medicinal ingredients: In addition to lansoprazole, each delayed-release capsule contains the following non-medicinal ingredients: D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 3, gelatin, hydroxypropyl cellulose, hypromellose, macrogols, maize starch, magnesium carbonate, methacrylic acid-ethyl acrylate copolymer, polysorbate 80, silica colloidal anhydrous, sucrose, sugar spheres, talc, titanium dioxide.

Dosage Form and Packaging
LANSOPRAZOLE is available as 30 mg pink cap-black body capsules imprinted with “30” in white ink on the body and containing white to off white pellets. The capsules are available in bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

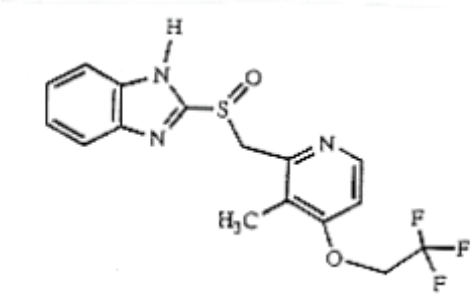
Proper Name: Lansoprazole

Chemical Name: 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-benzimidazole

Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$

Molecular Mass: 369.36 g/mol

Structural Formula:



Physicochemical Properties:

Lansoprazole is a white to brownish-white powder. Lansoprazole is freely soluble in dimethylformamide; slightly soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in water and hexane.

pK_a Values: $pK_{a1} = 8.84$
$pK_{a2} = 4.15$
$pK_{a3} = 1.33$

CLINICAL TRIALS

Comparative Bioavailability Studies

A blinded, randomized, single dose, two-way cross-over comparative bioavailability study of LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Dominion Pharmacal) versus PREVACID® (lansoprazole) 30 mg delayed-release capsules (Takeda Pharmaceuticals America Inc.) in 60 healthy adult mate volunteers was conducted under fasting conditions. Bioavailability data were measured and the results from 54 subjects are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA UNDER FASTING CONDITIONS

Lansoprazole (1 X 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90 % Confidence Interval (%)
AUC_T (ng.h / mL)	3419.827, 4520.886 (80.1)	3597.222 4606.701(76.2)	95.1	87.98 -102.74
AUC_I (ng.h / mL)	3483.413 4643.675 (82.5)	3670.424 4745.526 (78.5)	94.9	87.93 – 102.46
C_{max} (ng / mL)	1119.929 1214.787 (38.1)	1155.172 1225.902 (33.1)	97.0	88.58 -106.20
T_{max}§ (h)	1.750 (0.833 - 3.000)	1.625 (0.833 – 4.500)		
$T_{½}$€ (h)	2.112 (68.7)	2.180 (73.4)		

* LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Dominion Pharmacal)

† PREVACID ® (lansoprazole) 30 mg delayed-release capsules (Takeda Pharmaceuticals America Inc.) were purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV%) only

A blinded, randomized, single dose, two-way cross-over comparative bioavailability study of LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Dominion Pharmacal) versus PREVACID® (lansoprazole) 30 mg delayed-release capsules (Takeda Pharmaceuticals America Inc.) in 130 healthy adult male volunteers was conducted under fed conditions. Bioavailability data were measured and the results from 124 subjects are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA UNDER FED CONDITIONS

Lansoprazole (1 X 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90 % Confidence Interval (%)
AUC_T (ng.h / mL)	1617.533 2496.378 (101.1)	1723.605 2602.731 (106.4)	93.8	85.24 – 103.26
AUC_I (ng.h / mL)	1711.003 2650.268 (104.0)	1828.964 2777.700 (110.7)	93.8	85.37 – 102.96
C_{max} (ng / mL)	423.698 540.997 (65.1)	419.276 530.789 (68.7)	101.0	91.01 – 112.19
T_{max}§ (h)	4.000 (2.000-8.000)	3.667 (1.667-6.000)		
$T_{½}$€ (h)	2.106 (77.4)	2.231 (79.3)		

* LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Dominion Pharmacal).

† PREVACID® (lansoprazole) 30 mg delayed-release capsules (Takeda Pharmaceuticals America Inc.) were purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV%) only

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. After a single dose, 45% and 39% of patients treated with lansoprazole 15 mg and lansoprazole 30 mg, respectively, reported no day heartburn compared to 19% of patients receiving placebo. Likewise, 61% and 51% of patients treated with lansoprazole 15 mg and lansoprazole 30 mg, respectively, reported no night heartburn compared to 31% of patients receiving placebo. Data for frequency and severity for the 8-week treatment period were as summarized in Figure 1 and Figure 2 and Table 11.

Figure 1: **Mean Severity of Day Heartburn by Study Day for Evaluable Non-Erosive GERD Patients (3=Severe, 2=Moderate, 1=Mild, 0=None). Study M95-300**

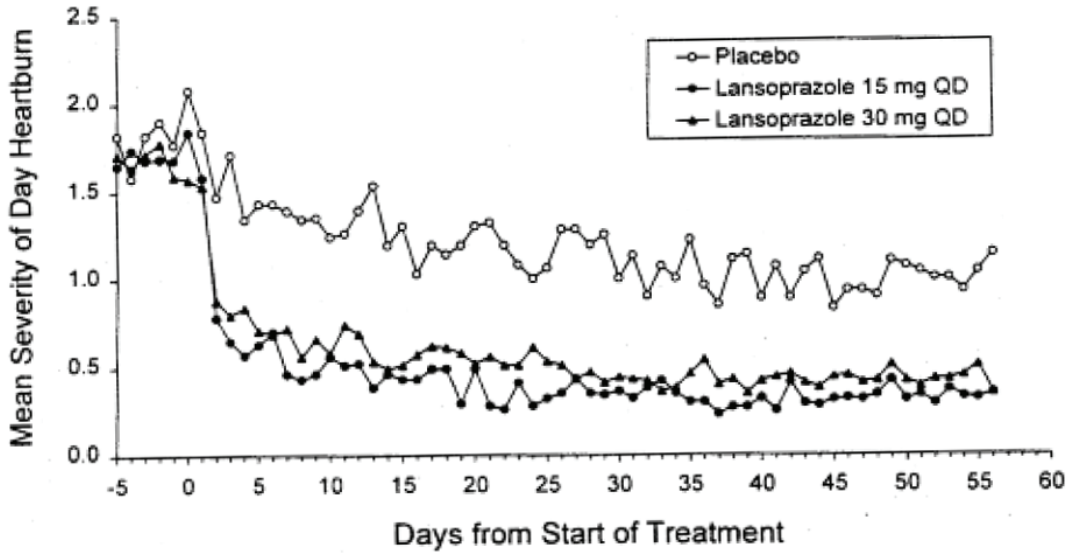


Figure 2: **Mean Severity of Night Heartburn by Study Day for Evaluable Non-Erosive GERD Patients (3=Severe, 2=Moderate, 1=Mild, 0=None). Study M95-300**

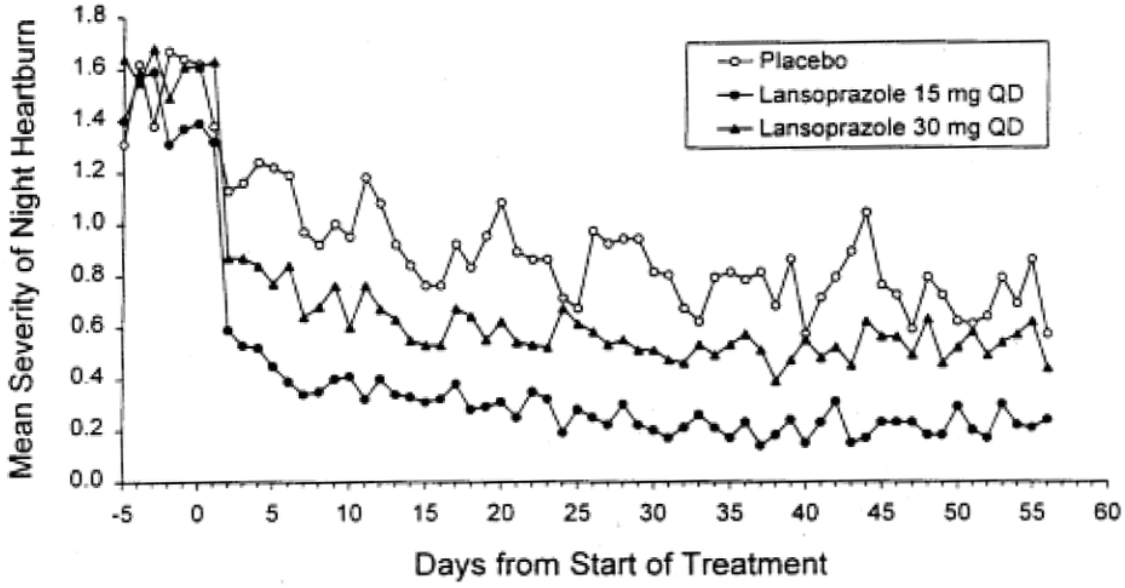


Table 11 Frequency of Heartburn at Week 1, Week 4, and Week 8 in Non-Erosive GERD Patients (Intent-to-Treat)			
Variable	**Placebo (n=43)**	**Lansoprazole 15 mg (n=80)**	**Lansoprazole 30 mg (n=86)**
% of Days without Heartburn (Median)			
Week 1	0	71*	46*
Week 4	11	81*	76*
Week 8	13	84*	82*
% of Nights without Heartburn (Median)			
Week 1	17	86*	57*
Week 4	25	89*	73*
Week 8	36	92*	80*
* ($p<0.01$) versus placebo.			

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

‡ In Canada, ranitidine is not indicated for the treatment of symptomatic GERD.

Reflux 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 12.

Table 12 Reflux Esophagitis Healing Rates				
Week	**Lansoprazole 15 mg q.d. (N=69)**	**Lansoprazole 30 mg q.d. (N=65)**	**Lansoprazole 60 mg q.d. (N=72)**	**Placebo (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%
* ($p\leq0.001$) versus placebo. † ($p\leq0.05$) versus Lansoprazole 15 mg.				

In this study, all lansoprazole delayed-release capsules 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 suggest 30 mg q.d. as the recommended dose.

Lansoprazole delayed-release capsules were also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflux esophagitis. Lansoprazole

delayed-release capsules at a dose of 30 mg were significantly more effective than ranitidine 150 mg b.i.d. as shown in Table 13.

Table 13
Reflux Esophagitis Healing Rates

Week	Lansoprazole 30 mg q.d. (N=115)	Ranitidine 150 mg b.i.d. (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 lansoprazole delayed-release capsules reported less day and nighttime heartburn and took less antacid tablets for fewer days than patients taking ranitidine 150 mg b.i.d.

In the two trials described and in several smaller studies involving patients with moderate to severe esophagitis, lansoprazole delayed-release capsules produced healing rates similar to those shown above.

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of lansoprazole delayed-release capsules were compared with ranitidine 150 mg b.i.d. 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. Lansoprazole delayed-release capsules 30 mg were more effective than ranitidine 150 mg b.i.d. in healing reflux esophagitis and the percentage of patients with healing are presented in Table 14.

This study does not constitute a comparison of the effectiveness of histamine H_2-receptor antagonists with lansoprazole delayed-release capsules as all patients had demonstrated unresponsiveness to the histamine H_2-receptor antagonist mode of treatment. It does indicate, however, that lansoprazole delayed-release capsules may be useful in patients failing on a histamine H_2-receptor antagonist.

Table 14
Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H_2-Receptor Antagonist Therapy

Week	Lansoprazole 30 mg q.d. (N=100)	Ranitidine 150 mg b.i.d. (N=51)
4	74.7%*	42.6%
8	83.7%*	32.0%

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

Pediatrics

Children 1 to 11 years of age

In an uncontrolled, open-label, U.S. multicenter study, 66 children (1 to 11 years of age) with GERD (58% had nonerosive GERD and 42% had erosive esophagitis, assessed by endoscopy) were assigned, based on body weight, to receive an initial dose of either lansoprazole 15 mg q.d. if ≤ 30 kg or lansoprazole 30 mg q.d. if >30 kg administered for 8 to 12 weeks. The lansoprazole dose was increased (up to 30 mg b.i.d.) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. Some children benefited from a dosage increase (up to 60 mg daily) based on efficacy results.

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 based on endoscopy (Table 15).

Table 15
Improvement in Overall GERD Symptoms (1 to 11 years)

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] Healing Rate	81% (22/27) 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 patients

Median fasting serum gastrin levels increased 89% from 51 pg/mL at baseline to 97 pg/mL [interquartile range (25^{th} to 75^{th} percentile) of 71 to 130 pg/mL] at the final visit.

In this study, 15 mg and 30 mg doses of lansoprazole were safe and well tolerated in this pediatric population (1 to 11 years of age). Dose increases (up to 60 mg daily when required) were not associated with any increase in adverse events or with any apparent trend in adverse events. No clinically significant changes in laboratory values, vital signs values, or physical examination results were observed among these children over an 8- to 12-week period. The elevations seen in serum gastrin levels were consistent with those observed in adult studies. There were no clinically significant changes or trends observed based on gastric biopsy findings including the nonantral endocrine cell population, as measured by Grimelius-positive cell counts and modified Solcia classification for the duration of this study.

Children 12 to 17 years of age

In a Phase I, multicenter, randomized, double-blind trial, the pharmacokinetic profile of lansoprazole in adolescents 12 to 17 years of age was compared to that previously observed in healthy adults, and also the safety and pharmacodynamic profile of lansoprazole in adolescents with symptomatic GERD was evaluated. The study consisted of a 7-day Pretreatment Period and a 5-day Treatment Period. The adolescents were randomized in an equal ratio to lansoprazole

15 mg q.d. or lansoprazole 30 mg q.d. for 5 days administered prior to breakfast or the first meal of the day.

The results of this study demonstrated that the pharmacokinetics of lansoprazole are similar between the adolescents in this study and those previously observed in healthy adult subjects. Both C_{max} and AUC_{0-24} of lansoprazole increased proportionately with dose from 15 to 30 mg for oral administration q.d. for five days. A significant increase in average 24-hour intragastric pH after five days of lansoprazole 15 mg or 30 mg administration was observed for adolescents in this study, as was consistently observed in healthy adult subjects. The same was true for the percentage of time intragastric pH was above 3 and 4. In addition, the lansoprazole 30 mg q.d. regimen significantly increased the percentage of time the intragastric pH was above 5.

Subjects in both the lansoprazole 15 mg q.d. and lansoprazole 30 mg q.d. groups demonstrated improvement in symptoms of reflux disease despite receiving a short course of therapy. Additionally, 69% of the lansoprazole 15 mg q.d. subjects and 74% of the lansoprazole 30 mg q.d. subjects reported that their reflux symptoms were reduced during the short period of treatment with lansoprazole.

Long-Term Maintenance Treatment of Reflux Esophagitis

U.S. Studies

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 reflux esophagitis was significantly less in patients treated with lansoprazole delayed-release capsules than in patients treated with placebo over a 12-month period (Table 16).

Table 16
Endoscopic Remission Rates (U.S. Study)

Trial	Drug	No. of Patients	% in Endoscopic Remission 0 to 3 mo.	% in Endoscopic Remission 0 to 6 mo.	% in Endoscopic Remission 0 to 12 mo.
1	Lansoprazole 15 mg q.d.	59	83%*	81%*	79%*
	Lansoprazole 30 mg q.d.	56	93%*	93%*	90%*
	Placebo	55	31%	27%	24%
2	Lansoprazole 15 mg q.d.	50	74%*	72%*	67%*
	Lansoprazole 30 mg q.d.	49	75%*	72%*	55%*
	Placebo	47	16%	13%	13%

% = Life Table estimate
* ($p \leq 0.001$) versus placebo

Regardless of initial grade of reflux esophagitis, lansoprazole delayed-release capsules 15 mg and 30 mg were similarly effective in maintaining remission.

European Studies

The first study, a double-blind, multicenter, comparative prospectively randomized trial was conducted in patients with endoscopically confirmed healed esophagitis. Patients remained in remission significantly longer and the number of recurrences of reflux esophagitis was

significantly less in patients treated with lansoprazole delayed-release capsules than in patients treated with ranitidine over a 12-month period (Table 17).

Table 17
Endoscopic Remission Rates (European Studies)

Drug	No. of Patients	% in Endoscopic Remission 0 to 6 mo.	% in Endoscopic Remission 0 to 12 mo.
Lansoprazole 15 mg q.d.	80	81.1%*	66.1%*
Lansoprazole 30 mg q.d.	71	85.6%*	77.4%*
Ranitidine 300 mg b.i.d.	70	38.1%	29.8%

% = Life Table estimate
* ($p \leq 0.001$) versus ranitidine.

The second study, a double-blind, multicenter, randomised trial was conducted in patients with symptomatic and endoscopically confirmed esophageal stricture resulting from reflux esophagitis. A higher proportion of patients in the ranitidine group required re-dilatation during the 12-month period compared to the lansoprazole group, but this difference was not statistically significant (Table 18).

Table 18
Proportion of Patients Requiring Re-Dilatation (European Study)

Time	Proportion of Patients Requiring Re-Dilatation	
	Lansoprazole 30 mg q.d.	Ranitidine 300 mg b.i.d.
Month 6	31.4% (22/70)	40.8% (29/71)
Month 12	34.3% (24/70)	46.5% (33/71)

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
In three open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, lansoprazole delayed-release capsules 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.

The majority of patients studied were treated with lansoprazole between one to three years (Table 19). Initial doses were titrated to the individual patients need, and adjustments were necessary with time in some patients (see DOSAGE AND ADMINISTRATION). Lansoprazole delayed-release capsules were well tolerated at these high dose levels for prolonged periods (greater than four years in some patients). In most ZE patients, serum gastrin levels were not modified by lansoprazole delayed-release capsules. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of lansoprazole therapy.

Consistent with its control of acid secretion, lansoprazole was also effective in controlling the associated symptoms experienced due to increased gastric acid secretion. In addition to symptom control, lansoprazole was effective in healing DU's and/or GU's and erosive RE.

Table 19 Summary of the Major Results from the Principal ZES Studies			
	Study 1 (N=21)	**Study 2 (N=30)**	**Study 3 (N=6)**
No. of Patients Entering Maintenance Phase	**20**	**28**	**6**
Age (yr) Mean Range	 49 27-68	 50 22-88	 56 35-76
Gender (No. of Patients) Male Female	 10 11	 20 10	 5 1
Baseline BAO (mEq/h) Mean Range	 38.7 9.9-143.9	 32.6* 5.5-96.5	 31.8 13.4-64.5
Duration of Follow-up (yr) Mean Range	 2.6 0.5-3.8	 1.4 0.2-2.5	 1.2 0.1-1.6
No. of Patients with Follow-Up > than: 1 year 2 years 3 years	 17 15 9	 17 11 0	 4 0 0
No. of Patients with a Final Maintenance Visit+	20	25	5
Lansoprazole Dose/24h at Final Maintenance Visit Median Range	 60 30-120	 60 30-180	 15 7.5-150
% (No. Patients with BAO <10 mEq/h) at Final Maintenance Visit	95 (19)	96 (24)	100 (5)
Percent of Patients with Dose Change from End of Titration to Final Maintenance Visit Increase Decrease No Change	 15 45 40	 20 40 40	 20 60 20
* Baseline BAO given is for the 18 ZES patients without prior gastrectomy. The baseline BAO for the remaining patients in Study 2 are as follows:			
		ZES w/Prior Gastrectomy (n=4)	Hypersecretors (n=8)
Baseline BAO (mEq/h) Mean Range		 9.2 5.5-17.0	 21.2 8.2-36.5
+ Final maintenance visit is defined as the last available visit incorporated into the interim data summary.			

DETAILED PHARMACOLOGY

In Animals

Pharmacodynamics

Studies of the preclinical pharmacology of lansoprazole have delineated its mechanism of action with *in vitro* investigations and have demonstrated *in vivo* efficacy. The orally administered compound appears to gain access to gastric parietal cells as the uncharged parent with conversion in the secretory canaliculus to charged metabolites that bind directly to a sulfhydryl group on the

canalicular (H^+, K^+)-ATPase. *In vivo* comparisons with the histamine H_2-receptor antagonist (H_2-RA) famotidine have revealed that in preventing ulcer induction or in accelerating healing, famotidine shows greater potency but is not as universal in its effect as lansoprazole. Famotidine fails to suppress acid secretion induced by stress and deoxyglucose and also fails to prevent gastric lesions induced by ethanol. Further, famotidine is significantly less potent than lansoprazole in preventing esophagitis resulting from reflux and decreased mucosal resistance.

These data suggest that lansoprazole has a potency profile comparable to that of another proton-pump inhibitor, omeprazole; while potency with respect to H_2-RAs may not be as great, more comprehensive suppression of acid secretion is achieved with associated acceleration of lesion healing.

General pharmacology investigations have not revealed identifiable tendencies in animal models for lansoprazole to induce untoward side effects. No contraindicated effects could be detected in the gastrointestinal (GI) system. Smooth muscle contraction and GI transit are unaffected by lansoprazole at doses 200 times greater than those anticipated in humans. Beneficial effects of the compound have been observed on gastric hemodynamics in experimental shock. No notable neuropharmacologic results have been observed. No effects of lansoprazole have been observed on muscle relaxation, anticonvulsant activity, analgesia, or hypothermic responses. Both central and autonomic responses are also free of detectable effects of the compound.

Results on cardiovascular pharmacology are, similarly, without physiologic significance. No notable effects were observed on blood pressure, heart rate, or respiration at doses in excess of 600-fold greater than the anticipated dose in humans. Similarly, water and electrolyte balance are unperturbed by lansoprazole.

The combination of both *in vitro* and *in vivo* efficacy for this inhibitor of the gastric proton pump has been demonstrated to be comparable to another member of its class, omeprazole. Its efficacy profile has been found superior to a representative H_2-RA, famotidine. Notable absence of untoward side effects has been demonstrated over a wide range of animal species and suggests a highly specific site of action in the acid secretory compartment of the gastric parietal cell.

Pharmacokinetics

After oral doses of ^{14}C-lansoprazole in gum arabic suspensions or in gelatin capsules, 27% of the radioactivity was absorbed in mice, 37% in rats, and 63 to 87% in dogs. However, due to degradation and hepatic metabolism of the absorbed dose, bioavailability was much lower, representing 4% in mice and rats and 22% in dogs. Peak levels of parent drug in mice, rats, and dogs were reached within two hours after dosing, and plasma concentrations generally increased with dose size. Considerable interanimal variability was found in monkeys, and C_{max} values occurred from 0.5 to six hours after a 50 mg/kg oral dose in gum arabic. Following an oral dose of lansoprazole, AUC values ranged from 10 to 1230 ng•h/mL in mice (1.5 to 50 mg/kg), 30 to 9639 ng•h/mL in rats (2 to 150 mg/kg), 450 to 8800 ng•h/mL in dogs (0.5 to 50 mg/kg), and 4750 ± 4990 ng•h/mL in monkeys (50 mg/kg). The half-life of lansoprazole ranged from 0.2 to 1.2 hours in mice and rats and had a tendency to increase with dose size; the half-life in dogs averaged 0.6 to 1.7 hours, and in monkeys was 3.3 hours. The AUC and C_{max} parameters were reasonably consistent after multiple doses of lansoprazole in mice and rats, were variable in

monkeys, and decreased appreciably in dogs. The pharmacokinetic data for lansoprazole is summarized in Table 20. (For pharmacokinetic parameters of lansoprazole in humans, see ACTION AND CLINICAL PHARMACOLOGY.) Following oral or IV administration of a 2 mg/kg dose of racemic lansoprazole to rats and dogs, C_{max} and/or AUC values were about two to threefold greater for the (+) enantiomer than the (-) enantiomer. *In vitro* studies with racemic lansoprazole and the individual isomers using rat and dog liver 9000 x g supernatants suggested that the (-) isomer is metabolized more rapidly than the (+) isomer, resulting in lower plasma concentrations of the (-) isomer. Both enantiomers apparently inhibit acid secretion to about the same extent.

Circulating metabolites in rats and dogs included the sulfide (M-I), benzimidazole (M-III), the 5-hydroxysulfide (M-IV), 5-hydroxylansoprazole (M-VI), the sulfone (M-VII), the 5-hydroxysulfone (M-IX) and the hydroxymethyl metabolite (M-X), (see Figure 3). Pharmacokinetic characterization of these metabolites has not been done. However, studies of total uncharacterized metabolites have demonstrated that, based on C_{max} values after oral doses, the plasma levels exceed those of parent drug by 1.3 to 19 fold in mice, rats, and dogs. The half-life of the metabolites averaged one to three hours in mice, and eight to 11 hours in rats and dogs.

Table 20
Summary of Pharmacokinetic, Metabolism and Excretion Data for Lansoprazole in Animals

Parameter	Mouse	Rat	Dog
Oral Doses (mg/kg)	*(1.5 - 50)*	*(2-150)*	*(0.5-50)*
Plasma			
Lansoprazole			
C_{max} (ng/mL)	30 - 1840	10 - 2872	350 - 3470
T_{max}(h)	0.17 - 0.34	0.25 - 2	0.25 - 2
$t_{½}$ (h)	0.2 - 1.1	0.3 - 1.2	0.6 - 1.7
AUC (ng•h/mL)	10 - 1230	30 - 9639	450 - 8800
Metabolites			
C_{max} (ng Eq/mL)	210 - 15600	140 - 4290	450 - 7490
T_{max} (h)	0.17 - 0.34	0.5 - 1	1 - 2
$t_{½}$ (h)	1.4 - 3.1	8 - 11.9	7.9 - 11.1
AUC (ng Eq•h/mL)	260 - 17370	1130 - 38100	4410 - 62700
Excretion			
Urine (% Dose)		17.9	12 - 24.6
Feces (% Dose)		81.0	67.5 - 83.7
Bile (% Dose)		59.6	42.6
Metabolism			
Urine (% Dose)			
Lansoprazole		0.1	0 - 0.1
M-II to M-V		1.4 - 1.9	0.2 - 1.5
M-VI to M-IX		0.2 - 1.3	0.2 - 1.3
M-X		3.6	1.3
Feces (% Dose)			
Lansoprazole		0.8	0 - 1.2
M-I, M-III		0.7 - 1.0	0.7 - 1.5
M-II		8.7	0 - 14.8
M-IV		18.5	14.9 - 33.4
M-V to M-X		0.6 - 1.7	0.7 - 3.5

Table 20 Summary of Pharmacokinetic, Metabolism and Excretion Data for Lansoprazole in Animals			
Bile (% Dose)			
Lansoprazole		0.2	
M-I to M-III		0.1 - 1.5	
M-IV		10.7	6.0
M-V,M-VII,M-VIII		0.6 - 1.0	
M-VI		1.8	8.0
M-IX		4.1	3.7
Metabolites M-I through M-X are identified in Figure 3.			

Protein Binding

Lansoprazole was extensively bound to plasma proteins. At lansoprazole concentrations ranging from 10 to 5000 ng/mL, protein binding ranged from 92 to 96% in rat and dog plasma. Binding of the drug to mouse plasma proteins has not been studied.

Distribution and Accumulation

The distribution and accumulation of lansoprazole in tissues have been studied in rats, and one accumulation study was done in mice. No tissue distribution studies have been reported in dogs. Lansoprazole was rapidly distributed throughout the body of rats after a 2 mg/kg oral dose, with relatively high concentrations in the intestine, stomach, liver, kidney, and thyroid. Tissue to plasma ratios of two to 35 were noted in these tissues. Concentrations in the brain and all other tissues examined were lower than circulating levels. After multiple oral doses (2 mg/kg/day) for seven days, radioactivity in plasma and tissues was slightly elevated, and the overall distribution patterns were similar. The cumulative excretion curves parallelled the administered dose, suggesting little accumulation of the drug in tissues with daily dosing. In both the single- and multiple-dose studies, most of the drug was cleared from all tissues except the thyroid after 72 hours. The tissue distribution pattern in mice 24 hours after a single, oral 1.5 mg/kg dose was comparable to that seen in rats. Accumulation of the dose in plasma and practically all tissues of mice and rats was observed after large oral doses of 50 mg/kg/day for 26 days.

Lansoprazole readily penetrated into the parietal cells of the gastric mucosa of rats and persisted for 24 hours. Levels of parent drug in the mucosa were two to fivefold greater than those in plasma up to six hours after a 2 mg/kg IV dose, supporting the concept that lansoprazole suppresses acid secretion by inhibiting the (H^+,K^+)-ATPase enzyme located in these cells.

Enzyme Induction and Inhibition

Daily, oral administration of a 150 mg/kg dose of lansoprazole to rats for five days resulted in a moderate induction of microsomal, mixed function oxidase enzymes in the liver. Microsomal protein, total cytochrome P-450, and cytochrome b_5 levels were increased 12 to 45%, while activities of p-nitroanisole O-demethylase and p-nitrophenyl glucuronyltransferase were elevated about two to threefold. Moreover, incubation of lansoprazole with rat liver microsomes (60 to 1500 mcg/g liver) inhibited the *in vitro* metabolism of aminopyrine, aniline, and p-nitroanisole from 8 to 71%. The data suggested that acute doses may inhibit some drug-metabolizing enzymes, while chronic doses induce their formation.

Metabolic Pathways

In vitro studies demonstrated that lansoprazole was preferentially metabolized by the liver in rats, but metabolic activity was also found in whole blood, kidney, and especially rat fecal contents. The drug is acid labile, and intestinal degradation has also been reported. A total of ten metabolites (designated as M-I to M-X) have been identified in biologic samples from rats and dogs. Many of the metabolites were found as sulfate or glucuronic acid conjugates. The metabolic scheme is illustrated in Figure 3.

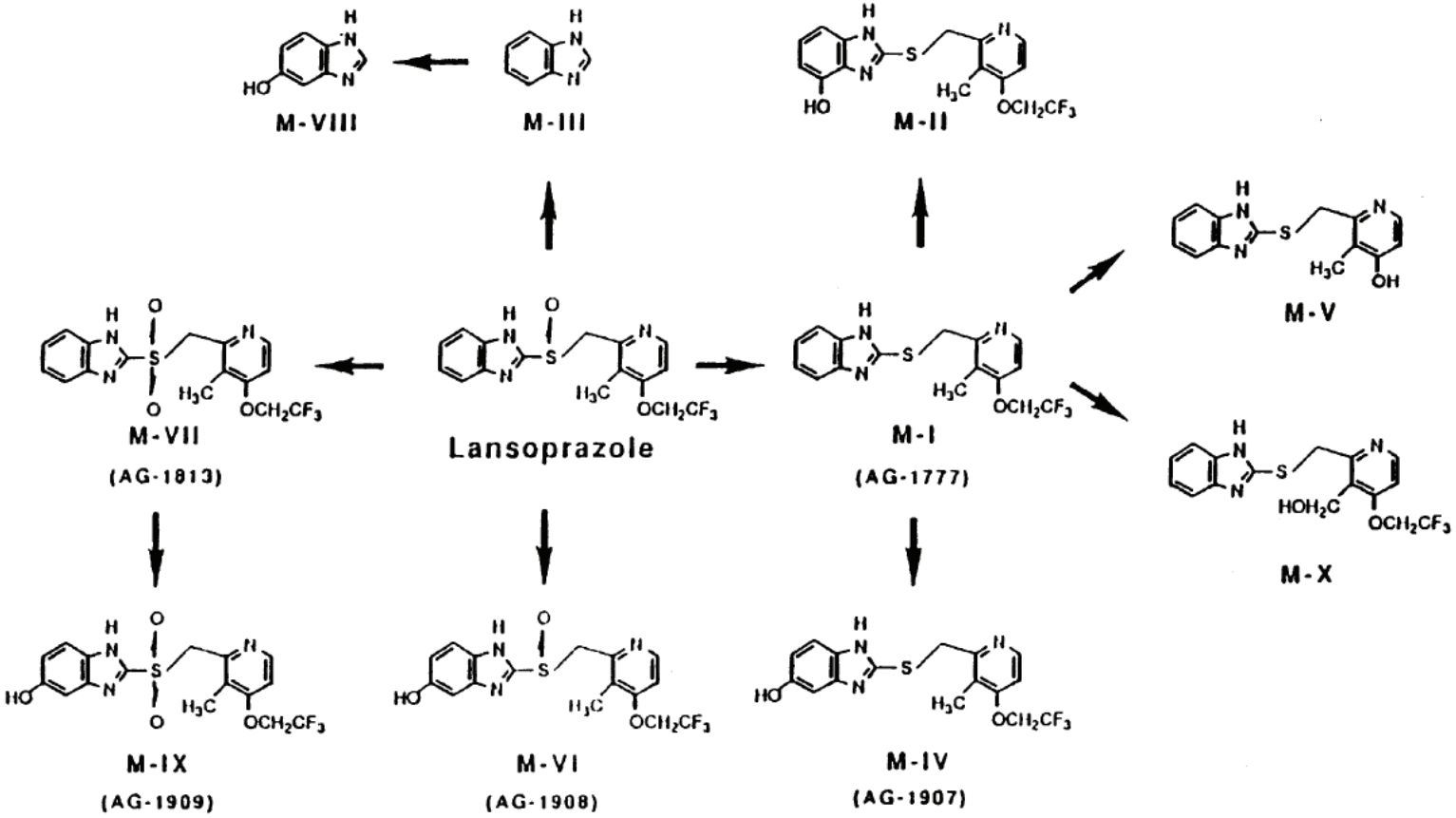


Figure 3: Postulated Metabolic Pathways of Lansoprazole in Rats and Dogs

Lansoprazole is metabolized by the following pathways: 1) reduction and oxidation of the sulfoxide group to form the sulfide (M-I) and sulfone (M-VII); 2) hydroxylation on the benzimidazole ring to give 6-hydroxysulfide (M-II), 5-hydroxysulfide (M-IV), 5-hydroxylansoprazole (M-VI), 5-hydroxybenzimidazole (M-VIII), and 5-hydroxysulfone (M-IX); 3) hydroxylation of the methyl group on the pyridine ring (M-X); 4) dealkylation (M-V); and 5) elimination of the pyridylmethylsulfinyl group to form benzimidazole (M-III).

Excretion

Both urinary and fecal excretion were involved in eliminating lansoprazole and its metabolites from the body. About 12 to 25% of the dose was found in the urine, while 68 to 84% was excreted into the feces, primarily via the bile. Metabolites M-II through M-X (free and conjugated) were found in the urine of rats and dogs and represented 0.2 to 3.6% of the dose. The sulfide (M-I) and free parent drug were not detected in urine.

Unchanged lansoprazole was a minor fecal component (approximately 1% of the dose), while the major metabolites were identified as the free 5-hydroxysulfide (M-IV) and the 4-hydroxysulfide (M-II), representing about 15 to 33 and 9 to 15% of the dose in rats and dogs, respectively. The remaining eight metabolites were also detected, and each accounted for 0.6 to 3.5% of the dose, but about half of the metabolites were not characterized. Metabolite profiles in rat bile showed that, except for the hydroxymethyl metabolite (M-X), all other identified metabolites were present. The 5-hydroxysulfide (M-IV), 5-hydroxylansoprazole (M-VI) and the 5-hydroxysulfone (M-IX) were major components of rat and dog bile, representing 6 to 11, 2 to 8, and 4% of the dose, respectively. As noted in the feces, many of the biliary metabolites have not been characterized. Excretion Data for lansoprazole are summarized in Table 21.

Table 21
Excretion Data for the Lansoprazole Dose in Animals and Humans

Species	Dose (mg/kg)	Route	Percent of the Carbon-14 Dose		
			Urine	Feces	Bile
Rat	2	PO	17.9	81.0	
	2-D	PO	16.7	81.5	
	2	ID	13.2	20.8	59.6
Dog	2	PO	12	83.7	
	0.5	PO	24.6*	67.5	
	0.5	IV	28.4*	63.9	
	0.5	IV			42.6
Human	ca. 0.43	PO	32.2	64.3	

* includes cagewash; D = daily dosing; PO = orally dosed; IV = intravenously dosed; ID = intraduodenally dosed

In Humans

Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2 antagonist properties, but 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. The inhibition of gastric acid secretion persists for up to 36 hours after a single dose. Thus, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

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 >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume. Lansoprazole also significantly reduced pentagastrin-stimulated acid output. In patients with hyper secretion 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.

In a crossover study comparing lansoprazole 15 and 30 mg to omeprazole 20 mg for 5 days, the following effects of lansoprazole on intragastric pH were noted (Table 22).

Table 22
Mean Antisecretory Effects of Lansoprazole After Multiple Daily Dosing

Parameter	Baseline Value	Lansoprazole 15 mg	Lansoprazole 30 mg	Omeprazole 20 mg
Mean 24-hour pH	2.05	4.03[+]	4.91[*]	4.16[+]
Mean Nighttime pH	1.91	3.01[+]	3.80[*]	3.04[+]
% Time Gastric pH >3	18	59[+]	72[*]	61[+]
% Time Gastric pH >4	12	49[+]	66[*]	51[+]

Note: An intragastric pH of >4 reflects a reduction in gastric acid by 99%
[*] ($p < 0.05$) versus baseline, lansoprazole 15 mg and omeprazole 20 mg
[+] ($p < 0.05$) versus baseline only

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with lansoprazole 30 mg, 2 to 3 hours with lansoprazole 15 mg, and 3 to 4 hours with omeprazole 20 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1 to 2 hours postdosing with lansoprazole 15 mg and omeprazole 20 mg.

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

Other gastric and esophageal effects

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 17% in blood flow in the antrum, pylorus and duodenal bulb was seen. Lansoprazole did not significantly affect gastric emptying of liquids, but significantly slowed the gastric emptying of

digestible solids. Esophageal motility and lower esophageal sphincter tone were not modified by lansoprazole therapy. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection.

Enterochromaffin-like cell effects / Carcinoid formation

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day about 1 to 40 times the exposure on a body surface (mg/m^2) basis, of a 50 kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). 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 body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rats. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one year toxicity study. Hypergastrinemia secondary to prolonged and sustained hypochlorhydria, such as that induced by high doses of ranitidine, omeprazole, and surgery, has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumors develop.

Gastric biopsy specimens from the body of the stomach from over 300 patients treated continuously with lansoprazole for eight weeks to 120 weeks have not shown evidence of ECL effects similar to those seen in rats. Longer term data are needed to rule out the possibility of an increased risk for the development of gastric carcinoid tumors in patients receiving long-term therapy with lansoprazole.

Serum gastrin effects

Fasting serum gastrin levels increased modestly during the first two to four weeks of therapy with 15 to 60 mg of lansoprazole. This increase was dose-dependent. Median serum gastrin values in over 2100 patients treated with lansoprazole 15 to 60 mg remained within normal range and generally increased 1.5 to twofold. Gastrin values 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 included testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), and somatotropic hormone (STH). Lansoprazole 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 dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rats. These findings are rat specific.

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. Lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function. No lansoprazole-related visual adverse events were noted in over 7000 patients treated in Phase I to Phase III clinical trials worldwide. No visual toxicity was observed among 63 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 68 months. Other rat-specific findings after a lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

TOXICOLOGY

In Animals

Single-Dose Studies
In an acute toxicity study, lansoprazole administered via the oral (PO), subcutaneous (SC) and intraperitoneal (IP) routes was studied in groups of 5M, 5F Wistar rats and 5M, 5F ICR mice. Lansoprazole was suspended in 5% gum arabic adjusted to pH 7 for administration by all three routes. The LD_{50} by the PO route in both rats and mice was greater than 5000 mg/kg, the highest dose tested. There were no deaths in either study. The only clinical sign noted was dark brown urine in mice.

By the SC route, the LD_{50} was again greater than 5000 mg/kg, the highest dose tested. Again, there were no deaths in either species. Scratching at the injection site and abdominal stretching were observed in mice. There were no clinical signs in rats. Drug remnants were seen at the injection sites in both species.

Finally, when lansoprazole was administered via the IP route, there were no deaths in mice at 5000 mg, but several rats of both sexes died within two days after dosing. Surviving rats were normal by the second day after dosing. The LD_{50} in rats was approximately 5000 mg. Abdominal stretching, decreases in activity, respiratory depression, and hypotonia of abdominal muscles were seen in rats and mice. Dark purple urine was also seen in mice. At autopsy, drug remnants were seen in the peritoneal cavity in animals of both species. Discoloration of the liver was also seen in rats that died at 5000 mg. These studies demonstrated that lansoprazole has a very low degree of toxicity when given as a single dose by either the oral, SC, or IP routes.

In an acute toxicity study of several metabolites, a contaminant, and partially degraded lansoprazole (40°C and 75% relative humidity for six months) were determined in ICR mice. The compounds and the routes tested were pyridyl-oxide derivative (PO), sulfonyl derivative or metabolite VII (PO and IP), thio derivative or metabolite I (PO and IP), 5-hydroxy derivative or

metabolite VI (IP), and partially degraded lansoprazole (PO). There were no deaths, and the LD_{50} values in all cases were therefore greater than 5 g/kg, the limit dose. With oral administration, clinical signs were seen only with partially degraded lansoprazole. These included decreased activity, respiratory depression, hypo-irritability (decreased responsiveness), ataxia, and flattened posture (prostration). With IP administration, decreased activity, hypo-irritability, and respiratory depression were seen with metabolites VI and VII. In addition, with metabolite VII, chromaturia (dark purple urine) and soft feces or diarrhea were seen. These findings are all similar to the results of previous acute toxicity studies with lansoprazole. Therefore, none of the tested compounds were more toxic than lansoprazole itself.

In a single-dose study, two male beagle dogs per group (fasted for 18 hours) were given lansoprazole orally by gavage at doses of 500, 1000, and 2000 mg/kg. The drug was suspended in 5% gum arabic, pH 7. The dogs were observed for 15 days after dosing and subjected to necropsy. Organ weights and histopathologic assessments of selected organs were obtained. There were no deaths, no treatment-related clinical signs, no effects on body weight or food consumption, no effects on weights of major organs, and no treatment-related gross or histopathologic changes. Therefore, a single dose of 2000 mg/kg was non-toxic. Higher dosing was not justified for humane reasons.

Multidose Studies

In a three-month study, lansoprazole was given by oral gavage to groups of ten male and ten female CD-1 mice at dosages of 0, 15, 50, and 150 mg/kg/day. The vehicle was 5% gum arabic. Clinical signs, body weight, and food consumption were monitored. At the end of the study, blood was collected for hematology and biochemistry measurements. All animals were necropsied. Histologic evaluations were conducted on high-dosage and control animals, and stomachs were evaluated histologically in all animals.

There were no treatment-related deaths and no effects on clinical signs, body weight, food consumption, hematology, or serum chemistry variables. There were no treatment-related gross pathologic changes. Stomach weights were increased, and hyperplasia/hypertrophy of the glandular stomach was seen histologically at 50 and 150 mg/kg/day. These changes were secondary to the pharmacologic activity of the compound.

In a 13-week study, lansoprazole was given by oral gavage to groups of 10 male and 10 female CD-1 mice at dosages of 0, 150, 300, 600, 1200, and 2400 mg/kg/day. The drug was suspended in 5% gum arabic, pH 7. There were three possibly drug-related deaths at 2400 mg/kg/day. The only clinical sign observed was purple urine seen in all drug-treated groups. There were slight decreases (approximately 10 to 13% relative to controls) in hematocrit, hemoglobin, and erythrocyte counts in all drug-treated groups. Neutrophils were slightly decreased in drug-treated females. Total serum protein was decreased at 300 mg/kg/day or more. Stomach weights were increased in all drug-treated groups. Liver weights were increased at 300 mg/kg/day or more. Testis weights were decreased at 1200 and 2400 mg/kg/ day. At necropsy, the glandular stomach appeared thickened, and erosions of the mucosa were evident at all dosages. The testes appeared small at 1200 and 2400 mg/kg/day. Histologically, hyperplasia and vacuolation were seen in the gastric fundic mucosa in all drug-treated groups. A mild, chronic gastritis was seen at

300 mg/kg/day or more. Hepatocellular hypertrophy and vacuolation were seen at 150 mg/kg/day or more, and a brown pigment was seen in the liver mainly at 2400 mg/kg/day. Seminiferous tubular atrophy and aspermatogenesis were seen with increased incidence at 1200 and 2400 mg/kg/day. Reduced amount of sperm was seen in the epididymides at 1200 mg/kg/day or more. A no-toxic-effect dosage was not determined in this study. The MTD was judged to be in the range of 300 to 600 mg/kg/day.

In a three-month study, lansoprazole was administered by gavage to groups of 15 Sprague-Dawley rats/sex at dosages of 0, 5, 15, 50, and 150 mg/kg/day seven days per week. The drug was suspended in 5% gum arabic, pH 7.

There were no deaths and no behavioural signs of toxicity. Body weight was decreased in males at 150 mg/kg/day. There was no effect on food consumption. Hemoglobin and mean cell hemoglobin were decreased in females at 50 mg/kg/day or more, and in males at 150 mg/kg/day. Hematocrit was also decreased in males and females, and mean erythrocyte volume was decreased in males at 150 mg/kg/ day. Total leukocyte counts were increased in females at 50 mg/kg/day or more. Serum total protein and globulin were decreased, and A/G ratio increased in males at 150 mg/kg/day. There were no gross lesions noted at necropsy. Stomach weight was increased at 15 mg/kg/day or more. Liver weights were increased in females at 15 mg/kg/day or more. Thyroid and uterus weights were increased at 150 mg/kg/day. Thymus weights were decreased at 50 mg/kg/day or more. Histologically, thymic atrophy was observed at 15 mg/kg/day or more. In the stomach, increased chief cell hypertrophy, eosinophilia and single cell necrosis, eosinophilic material in gastric glands, and increased squamous cell hyperplasia and hyperkeratosis at the junction of the glandular and non-glandular mucosa were observed at 50 mg/kg/day or more.

Toxicity was demonstrated by decreased body weight in males, hematologic changes, decreases in serum protein, thymic atrophy, and chief cell necrosis. Hematologic changes and chief cell necrosis occurred at 50 mg/kg/day or more. Thymic atrophy was observed at 15 mg/kg/day or more. Therefore, the no-toxic-effect dosage was 5 mg/kg/day.

In a four-week study, lansoprazole was administered orally by gavage to ten Wistar rats/sex/group at dosages of 0, 15, 50, and 150 mg/kg/day (seven days/week). The drug was suspended in 5% gum arabic for administration.

There were no deaths and no behavioural signs of toxicity. Body weight gain was suppressed in males by 7% at 50 mg/kg/day and by 15% at 150 mg/kg/day. Food consumption was decreased in both sexes at 150 mg/kg/day and in males at 50 mg/kg/day. Hepatic drug-metabolizing enzymes, aminopyrine-N-demethylase and aniline hydroxylase activities, were increased at 150 mg/kg/day. Thymic atrophy was noted at necropsy at 150 mg/kg/day. Thymic weights were decreased 21 to 27% at 50 mg/kg/day and 48 to 49% at 150 mg/kg/day. Liver weights were increased at 50 and 150 mg/kg/day. Adrenal weights were increased in females at 150 mg/kg/day. Histologically, centrilobular hepatocellular hypertrophy was seen in the liver at 150 mg/kg/day. An increase in smooth endoplasmic reticulum in the liver was seen by electron microscopy. In the stomach, vacuolation of parietal cells and apical eosinophilia of chief cells

were seen histologically, while dilation of parietal cell tubulovesicles was seen by electron microscopy at 150 mg/kg/day.

Toxicity was demonstrated by decreases in body weight gain and food consumption, and thymic atrophy at 50 mg/kg/day or more. The no-toxic-effect dosage was 15 mg/kg/day.

In a 13-week study, lansoprazole was administered to Wistar rats (ten/sex/group) at dosages of 0, 5, 15, and 50 mg/kg/day, seven days/week. The drug was suspended in 5% gum arabic adjusted to pH 7.

There were no deaths and no behavioral signs of toxicity. Body weight was decreased 5 to 6% in both sexes by the end of the study at 50 mg/kg/day. There were no treatment-related effects on hematology, serum chemistry, or urinalysis variables. Measurements of plasma T_3, T_4, and TSH in the high-dosage and control animals revealed no differences between the two groups. Statistically significant elevations in serum gastrin, determined 20 hours post-dosing at the end of the study, were obtained in females at 15 mg/kg/day or more and in males at 50 mg/kg/day. At necropsy, the stomach glandular mucosa was observed to be thickened in both sexes at 50 mg/kg/day and in females at 15 mg/kg/day. Stomach weights were increased at all dosages.

Thymus and submaxillary weights were decreased at 50 mg/kg/day. Histologically, centrilobular hepatocellular hypertrophy was seen in the liver at 50 mg/kg/day. In the stomach, increased argyrophil cell density, hypertrophy of parietal cells, and sporadic necrosis of chief cells were seen at 50 mg/kg/day. Chief cell eosinophilia, hypertrophy, and hyperplasia were seen at all dosages. Dilation of tubulovesicles in parietal cells and small, dense granules in chief cells were seen by electron microscopy at 50 mg/kg/day.

Toxicity was demonstrated by decreased body and thymus weights and chief cell necrosis at 50 mg/kg/day. The no-toxic-effect dosage was 15 mg/kg/day.

In a 13-week study, male Wistar rats were given daily dosages of 50 mg/kg/day lansoprazole orally by gavage, and were then allowed to recover without treatment for periods of four, 13, or 26 weeks. A control group was given vehicle (5% gum arabic, pH 7). There were ten rats for each of the necropsy intervals (13 weeks treatment, four weeks recovery, 13 weeks recovery, and 26 weeks recovery).

The changes observed at the end of 13 weeks of treatment were similar to those seen at 50 mg/kg/day in the previous 13-week study. In this study, gastrin-secreting cells (G cells) were determined in the stomach pylorus by immunohistochemical staining. The volume density of G cells was found to be increased after 13 weeks of treatment. All of the changes were found to be reversible after four weeks recovery without treatment except stomach weight, changes in chief cells, and the increase in argyrophil cells. The increase in argyrophil cells was reversible after 13 weeks of recovery. Necrosis, eosinophilia, hypertrophy, and hyperplasia of chief cells showed partial reversal after four and 13 weeks recovery and complete reversal after 26 weeks, recovery. Stomach weight in the treated group was comparable to controls after 26 weeks of recovery.

In a six-month study, lansoprazole was given to Sprague-Dawley rats (12/sex/group) at dosages of 0, 2, 10, and 50 mg/kg/day, seven days/week. The drug was suspended in 5% gum arabic, pH 7, and administered orally by gavage.

There were no treatment-related deaths, no behavioral signs of toxicity, no effects on body weight or food consumption, and no treatment-related changes in serum chemistry or urinalysis variables. There was a transient decrease in hematocrit, mean erythrocyte cell volume, and mean erythrocyte cell hemoglobin at 50 mg/kg/ day after three months of treatment. This was not seen at the end of the study. Stomach weight was increased in females at all dosages and in males at 10 mg/kg/ day or more. Thymus weights were decreased at 50 mg/kg/day. Histologically, thymic atrophy was seen at 10 mg/kg/day or more. In the stomach, increased hypertrophy, eosinophilia, and single cell necrosis of chief cells and an increase in argyrophil cells were seen at 10 mg/kg/day or more. At 50 mg/kg/day, dilation of gastric glands and increased severity of inflammatory cell accumulation, squamous cell hyperplasia, and hyperkeratosis at the junction of the glandular and nonglandular mucosa were seen.

Toxicity was demonstrated by the hematologic changes at 50 mg/kg/day, thymic atrophy at 10 mg/kg/day or more, and chief cell necrosis at 10 mg/kg/day or more. The no-toxic-effect dosage was 2 mg/kg/day.

In a one-year study, lansoprazole was administered by oral gavage to Sprague-Dawley rats (30/sex/group) at dosages of 0, 1.5, 5, 15, and 50 mg/kg/day, seven days per week. The vehicle was 5% gum arabic adjusted to pH 7.

There were no treatment-related deaths and no behavioral signs of toxicity. Body weight gain was decreased in males at 50 mg/kg/day, but there was no effect on food consumption. Hematocrit and hemoglobin were decreased at 50 mg/kg/day. There were no treatment-induced changes in serum chemistry or urinalysis variables. Stomach weight was increased at 5 mg/kg/day or higher. Liver weight was increased in females, while thymus weight was decreased in males at 50 mg/kg/day. Histologic evidence of thymic atrophy was also seen at 50 mg/kg/day. In the stomach, hypertrophy, eosinophilia and necrosis of chief cells was seen at 5 mg/kg/ day or more. Dilated gastric glands and increased incidence of argyrophil cells were seen at 15 mg/kg/day or more. Increased severity of inflammatory cells, squamous hyperplasia, and hyperkeratosis at the junction of the glandular and nonglandular mucosa was seen at 50 mg/kg/day. In the testis at 50 mg/kg/day, an increased incidence of Leydig (interstitial) cell hyperplasia was observed, and a single, benign Leydig cell tumor was found.

Toxicity was characterized by decreased body weight gain in males, decreases in hematocrit and hemoglobin, thymic atrophy, and Leydig cell hyperplasia at 50 mg/kg/day and by chief cell necrosis at 5 mg/kg/day or more. The no-toxic- effect dosage was 1.5 mg/kg/day.

In a six-month study, lansoprazole was given to four beagle dogs/sex/group in hard gelatin capsules at dosages of 0, 2, 10, and 50 mg/kg/day seven days per week.

There were no deaths or behavioral signs of toxicity. There were no treatment-related effects on body weight, food consumption, urinalysis, or ophthalmologic, electrocardiographic, or serum chemistry variables. One dog in the high-dosage group had a few atrioventricular (A-V) nodal escape beats; however, this sometimes occurs spontaneously in dogs and was not considered treatment related either by the sponsor or a consulting veterinary cardiologist. There were transient (present at three months but not at six months) decreases in hematocrit, hemoglobin, and erythrocyte counts in males at 2 and 10 mg/kg/day. Hematocrit, hemoglobin, mean cell hemoglobin, and mean erythrocyte volume were persistently decreased at both three and six months at 50 mg/kg/day in males. Total leukocyte count was increased in females at 50 mg/kg/day. There were no treatment-related findings at necropsy. Thymus weight was decreased in males at 50 mg/kg/day. Histologically, increased vacuolation of parietal cells in the gastric mucosa was seen at 10 mg/ kg/day or more.

Toxicity was characterized by hematologic changes and by decreased thymus weights at 50 mg/kg/day. The no-toxic effect dosage was 10 mg/kg/day.

In a 12-month study, Beagle dogs were given lansoprazole in hard gelatin capsules at dosages of 0, 1.5, 5, 15, and 50 mg/kg/day, seven days per week. There were four dogs/sex/group. There were two deaths, one male each at 15 and 50 mg/kg/day.

In surviving dogs, there were no behavioral signs of toxicity, no effects on body weight or food consumption, no treatment-related ophthalmoscopic findings, and no effects on serum chemistry or urinalysis variables. There were no ECG abnormalities in any of the dogs in the study. Total leukocyte counts were increased at 15 and 50 mg/kg/day; the increase at 15 mg/kg/day was transient (present at three months but not at later intervals) and in males only. Prostate weight was decreased at 5 mg/kg/day or more. Histologically, increased parietal cell vacuolization was seen at all dosages.

The cause of death or moribundity could not be determined for the two dogs that died. There were no indications from the other dogs in the study of any toxicity that could account for these deaths. Nevertheless, a conservative approach suggests that these two deaths be considered the result of toxicity due to drug treatment. Therefore, the no-toxic-effect dosage for this study was 5 mg/kg/day.

Pediatric studies

Two studies were conducted to evaluate the toxicity and toxicokinetics of lansoprazole in preadolescent rats and dogs. Selected dosages for the two species were identical to those used in adult animals in 4-week (Wistar strain) and 13-week (Sprague Dawley strain) studies in rats (Atkinson and Daly, 1986; Miyajima, 1986) and in a 13 week study in dogs (Chiba, 1989; Miyajima, 1989). Dosing of rats continued between weaning throughout adolescence (i.e., reproductive maturity). This age-range simulated the children age group of 2 to 12 year-olds. In dogs, dosing started 2 weeks after birth and continued for 4 weeks prior to weaning, followed by 7 weeks post-weaning for a total of 13 weeks. Evaluation of the stomach was emphasized, since part of the rationale for these studies was to evaluate the threshold for toxicity in target organ(s), particularly the stomach in younger premature animals and compare it to that of adult animals.

These studies also aimed at verifying any additional effects on developmental milestones due to dosing at these young ages.

The toxicity profile in preadolescent animals was not different from adult animals, and the no observable effect level (NOEL) doses were comparable between the two age groups. In the pediatric population the mean total initial lansoprazole dose is 0.87 mg/kg. Accordingly, the safety margin based on the NOEL of 5 mg/kg/day in two species was approximately 1 to 1.5-fold, based on plasma levels for lansoprazole only (excluding its metabolites); was approximately 1 to 3.5 fold based on surface area and was about 5.7- fold relative to this clinical dose.

Carcinogenesis

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day about 1 to 40 times the exposure on a body surface (mg/m^2) basis, of a 50 kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). 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 body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rats. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. Lansoprazole also induced a low, non-dose-related incidence of carcinoid tumours in the gastric mucosa in several dose groups (one female mouse in the 15 mg/kg/day group, one male mouse in the 150 mg/kg/day group, and 2 males and 1 female in the 300 mg/kg/day group). It also produced an increased incidence of liver tumours (hepatocellular adenoma plus carcinoma). The tumour incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) 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 body surface area).

Analysis of gastric biopsy specimens from patients after short-term treatment of proton pump inhibitors have not detected ECL cell effects similar to those seen in animal studies. Longer term studies in humans revealed a slight increase in the mean ECL-cell density, although there was no microscopic evidence of cell hyperplasia. Similar results were seen in the maintenance treatment studies, where patients received up to 15 months of lansoprazole therapy. Serum gastrin values increased significantly from their baseline values but reached a plateau after two months of

therapy. By one month post-treatment, fasting serum gastrin values returned to lansoprazole therapy baseline. Moreover, results from gastric biopsies from short-term, long-term and maintenance treatment studies indicate that there are no clinically meaningful effects on gastric mucosa morphology among lansoprazole-treated patients.

In a two-year study, lansoprazole was administered by oral gavage to Sprague-Dawley rats (60 males and 60 females per group) at dosages of 0, 1.5, 5, 15, and 50 mg/kg/day five days per week. Drug was suspended in 5% gum arabic (adjusted to pH 7.0 to 7.4).

Survival rates were 27 to 33% in males and 30 to 45% in females. The median survival time was 650 days in males and 683 days in females. Body weight gain was decreased at 50 mg/kg/day in both sexes and at all dosages in females. At the end of the study, body weight gains for high-dose males and females were both decreased 20% compared to controls. There were no other clinical signs of toxicity.

The incidence of interstitial (Leydig) cell hyperplasia was increased above concurrent and historical control levels at dosages of 15 and 50 mg/kg/day. The incidence of Leydig cell tumors was increased above concurrent control levels at 15 mg/kg/day and was at the high end of the historical control range at 50 mg/kg/day. The increases in incidence of Leydig cell hyperplasia and tumors were statistically significant at 15 and 50 mg/kg/day when compared to concurrent controls. Histologically, the Leydig cell tumors appeared similar to those that occur spontaneously in Sprague-Dawley rats and in aging Fischer 344 rats.

There were numerous changes in the gastric mucosa indicative of the pharmacologic effect of lansoprazole that were similar to those seen in previous toxicity studies. This included necrosis of chief cells which was seen at 5 mg/kg/day or more. A small increase in incidence of intestinal metaplasia was seen in both sexes at 50 mg/kg/day. Detailed examination of the intestinal metaplasia foci revealed the presence of Paneth cells, indicating complete type intestinal metaplasia in virtually every case. A single, carcinoid tumor was seen in the gastric fundic mucosa in a female at 50 mg/kg/day.

The decreases in body weight gain, necrosis of chief cells, and increased incidence of Leydig cell hyperplasia and tumors demonstrated that a MTD was administered.

The results suggest that oral administration of lansoprazole at dosages of 15 and 50 mg/kg/day for two years leads to higher levels of interstitial (Leydig) cell hyperplasia and tumors than found in control rats. There was no evidence for any other tumorigenic response due to drug administration.

Mutagenicity

Lansoprazole was not mutagenic in *in vitro Salmonella typhimurium* and *Escherichia coli* assays. A mouse micronucleus test at up to 5000 mg/kg (approximately 10,000 times the human dose) was negative for the induction of micronuclei. Results from a rat *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes were negative. Also, a mammalian cell mutagenesis assay was negative.

In vitro cytogenetics studies showed increased levels of aberrations consisting mainly of chromatid breaks which occurred only at cytotoxic concentrations. These cytotoxic concentrations were at least 50 to 60 times expected clinical blood levels of parent drug. Therefore, such concentrations will not be used in humans.

Retinal Atrophy

In two 24-month toxicology studies in albino rats, drug-related retinal changes were seen at dosages of 15 mg/kg/day or higher in females and 50 mg/kg/day or higher in males. These retinal changes were similar to the spontaneous age-related and/or light induced retinal changes normally seen in rats. However, at the higher dosages, higher incidence of diffuse atrophy involving central as well as peripheral retina and a higher incidence of bilateral retinal atrophy occurred.

Retinal atrophy was only observed in albino rats treated continuously for two years. These changes in rats are believed to be associated with the effects of taurine imbalance and phototoxicity in a susceptible animal model. This lesion was not seen in other species including mice dogs and monkeys.

Reproduction and Teratology

Six separate studies covering all phases of the reproductive process have been conducted. Treatment with lansoprazole caused a dose related reduction of implantations, viable fetuses and live births, and caused delayed parturition at 150 mg\kg\day.

However, lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

In two teratology studies, lansoprazole at dosages up to 300 mg/kg/day (approximately 600 times the human dose) was administered to rats on Days 6 to 17 of pregnancy. At higher dosages (150 to 300 mg/kg/day), only decreased fetal body weights were observed. Also at higher dosages, reduced ossification of vertebrae was indicative of fetal toxicity.

In rabbits, doses of lansoprazole up to 30 mg/kg/day (approximately 60 times the human dose) were administered on Days 6 to 18 of pregnancy. A treatment-related effect on fetal mortality at 30 mg/kg/day was noted, but there were no treatment related external, skeletal, or visceral abnormalities.

Lansoprazole is not considered to be teratogenic.

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PART III: CONSUMER INFORMATION

PrLANSOPRAZOLE
lansoprazole delayed-release capsules, USP

This leaflet is part III of a three-part "Product Monograph" published when LANSOPRAZOLE was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about LANSOPRAZOLE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
LANSOPRAZOLE is a medicine that is indicated in the treatment of conditions where the reduction of gastric acid secretion is required, such as:

- **Reflux esophagitis**
  A reflux esophagitis is an inflammation of the swallowing tube (esophagus) resulting from regurgitation of gastric contents into the esophagus. Because stomach contents are acidic, this may result in irritation of the esophagus.

- **Symptomatic gastroesophageal reflux disease (sGERD)**
  sGERD is a disorder that results from stomach acid moving backward from the stomach into the esophagus.

- **Pathological hypersecretory conditions**
  Pathological hypersecretory conditions are conditions in which the stomach produces too much acid which comes up into the esophagus and causes heartburn.

What it does:
LANSOPRAZOLE is a type of medication called a proton pump inhibitor, commonly known as PPI.

There are cells in the lining of your stomach that produce the acid your body uses during digestion. The burning pain from acid reflux disease is caused when this stomach acid backs up, or refluxes, into the esophagus.

LANSOPRAZOLE helps reduce stomach acid production. In doing so, LANSOPRAZOLE helps reduce the amount of acid backing up into your esophagus.

When it should not be used:
You should not take LANSOPRAZOLE if you have an allergy to lansoprazole or to any of the nonmedicinal ingredients in LANSOPRAZOLE (see What the nonmedicinal ingredients are below).

What the medicinal ingredient is:
Lansoprazole

What the nonmedicinal ingredients are:
D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 3, gelatin, hydroxypropyl cellulose, hypromellose, macrogols, maize starch, magnesium carbonate, methacrylic acid-ethyl acrylate copolymer, polysorbate 80, silica colloidal anhydrous, sucrose, sugar spheres, talc, titanium dioxide.

What dosage forms it comes in:
LANSOPRAZOLE is available in capsules, 30 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use LANSOPRAZOLE talk to your doctor or pharmacist:

- about all **health problems** you have now or have had in the past;
- about all **other medicines** you are taking, including non-prescription medicines, nutritional supplements, or herbal products;
- if you have or develop **severe diarrhea** as this may be a sign of a more serious condition;
- if you have **kidney problems**;
- if you have a **malignant gastric ulcer**;
- if you have **liver problems**;
- if you experience any **cardiovascular (e.g., heart) or neurological (e.g., brain) symptoms** including palpitations (rapid heartbeat), dizziness, seizures, and tetany (muscle condition with symptoms such as twitching, spasms, cramps and convulsions) as these may be signs of hypomagnesemia (low magnesium levels in the body);
- if you are taking **astemizole**†**, terfenadine**†**, cisapride**† (†not currently marketed in Canada)**, or pimozide;**
- if you have any **unusual** or **allergic reaction** (rash, difficulty breathing) to lansoprazole or any of the nonmedicinal ingredients in LANSOPRAZOLE (see What the nonmedicinal ingredients are), other medicines, foods, dyes, or preservatives.
- if you are **pregnant, trying to get pregnant or are breast-feeding**.

People who take multiple daily doses of proton pump inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist or spine. You should take LANSOPRAZOLE exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take LANSOPRAZOLE.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with LANSOPRAZOLE include:

- ampicillin esters
- atazanavir
- digoxin
- iron salts
- ketoconazole
- methotrexate

- sucralfate
- theophylline
- warfarin

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose of LANSOPRAZOLE is not the same for all the indications. Your doctor will tell you exactly which dose is better for your condition.

LANSOPRAZOLE should be taken daily before breakfast. Where the product may be used twice daily, it should be taken prior to breakfast and another meal. You should not chew or crush LANSOPRAZOLE capsules. LANSOPRAZOLE capsule should be swallowed whole with sufficient water.

Overdose:

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you miss a dose, take it as soon as you can. If it is almost time for your next dose, take only that dose. Do not take double or extra doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, LANSOPRAZOLE can cause side effects. However, most people do not have any side effects at all.

The following side effects have been reported (occurring between 1% and 10% in clinical trials): arthralgia (muscle pain), belching, constipation, diarrhea, dizziness, dry mouth, gas, headache, indigestion, insomnia, nausea, rash, vomiting, weakness. Talk to your doctor or pharmacist if any of these side effects persist or become bothersome.

If the following symptoms appear, consult your physician: bladder infection (pain, burning sensation upon urination) and upper respiratory tract infections (e.g., bronchitis, sinusitis, runny nose, sore throat).

Serious side effects from lansoprazole are not common.

After stopping your medication, your symptoms may get worse and your stomach may increase the acid production.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Uncommon (occurring between 0.2% and 1% in clinical trials)	Abdominal pain		✓	
	Severe diarrhea accompanied with blood and/or mucous			✓

This is not a complete list of side effects. For any unexpected effects while taking, LANSOPRAZOLE, contact your doctor or pharmacist.

HOW TO STORE IT

HOW DO I STORE LANSOPRAZOLE?
Keep LANSOPRAZOLE and all other medicines out of reach of children.

Store at room temperature (15°C - 30°C). Protect from light and moisture. Do not use beyond the expiration date.

GENERAL ADVICE ABOUT PRESCRIPTION MEDICINES:
Talk to your doctor or other health care provider if you have any questions about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a CONSUMER INFORMATION Leaflet. If you have any concerns about this medicine, ask your doctor. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Dominion Pharmacal at 1-888-550-6060

This leaflet was prepared by

Dominion Pharmacal
Montréal Québec
H4P 2T4

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