PRODUCT MONOGRAPH

Pr RIVA-LANSOPRAZOLE

Lansoprazole Delayed-Release Capsules, USP

15 mg and 30 mg

H^+, K^+ – ATPase Inhibitor

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 5
WARNINGS AND PRECAUTIONS 5
ADVERSE REACTIONS 12
DRUG INTERACTIONS 21
DOSAGE AND ADMINISTRATION 23
OVERDOSAGE 26
ACTION AND CLINICAL PHARMACOLOGY 27
STORAGE AND STABILITY 31
DOSAGE FORMS, COMPOSITION AND PACKAGING 32

PART II: SCIENTIFIC INFORMATION 33
PHARMACEUTICAL INFORMATION 33
CLINICAL TRIALS 34
DETAILED PHARMACOLOGY 52
TOXICOLOGY 60
REFERENCES 71

PATIENT MEDICATION INFORMATION 78

Pr RIVA-LANSOPRAZOLE

Lansoprazole Delayed-Release Capsules, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	All Nonmedicinal Ingredients
Oral	Delayed-release capsules/15 mg, 30 mg	D&C yellow No. 10, FD&C blue No. 1 (30 mg capsules only), FD&C green No. 3 (15 mg capsules only), FD&C red No. 3, gelatin, hydroxypropyl cellulose, hypromellose, macrogol, maize starch, magnesium carbonate, methacrylic acid-ethyl acrylate copolymer, polysorbate 80, silica colloidal anhydrous, sucrose, sugar spheres, talc, titanium dioxide.

INDICATIONS AND CLINICAL USE

NOTE: WHEN USED IN COMBINATION WITH ANTIMICROBIALS FOR THE ERADICATION OF *HELICOBACTER PYLORI* (*H. pylori*), THE PRODUCT MONOGRAPH FOR THOSE AGENTS SHOULD BE CONSULTED.

Adults

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

- Duodenal ulcer
- Gastric ulcer
- Reflux esophagitis including patients with Barrett's esophagus, and patients poorly responsive to an adequate course of therapy with histamine H_2-receptor antagonists.
- Healing of non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcer; treatment of NSAID-associated gastric ulcer in patients who continue NSAID use (controlled studies did not extend beyond 8 weeks)
- Reduction of risk of NSAID-associated gastric ulcers in patients with a history of gastric ulcers who require to continue taking a NSAID (a controlled study did not extend beyond 12 weeks)
- Symptomatic Gastroesophageal Reflux Disease (GERD); treatment of heartburn and other symptoms associated with GERD.
- Pathological hypersecretory conditions including Zollinger-Ellison Syndrome (see DOSAGE AND ADMINISTRATION).
- Eradication of *Helicobacter pylori* (*H. pylori*)

Triple Therapy: RIVA-LANSOPRAZOLE/Clarithromycin/Amoxicillin

Lansoprazole, in combination with clarithromycin plus amoxicillin as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and active duodenal ulcer disease. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

(FOR ADDITIONAL INFORMATION ON TRIPLE THERAPY FOR THE TREATMENT OF *H. PYLORI* INFECTION AND ACTIVE DUODENAL ULCER RECURRENCE, REFER TO THE HP-PAC PRODUCT MONOGRAPH.)

In patients with a recent history of duodenal ulcers who are *H. pylori* positive, eradication therapy may reduce the rate of recurrence of duodenal ulcers. The optimal timing for eradication therapy for such patients remains to be determined.

In patients who fail a therapy combination containing clarithromycin, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, an alternative therapy combination is recommended.

Resistance to amoxicillin has not been demonstrated in clinical studies with lansoprazole capsules and amoxicillin.

Table 1 summarizes the eradication rates for the *H. pylori* Triple Therapy treatment regimens.

Table 1. Eradication Rates for the *H. pylori* Triple Therapy Treatment

Treatment Regimen	Days/ Study No.	Evaluable (Per Protocol)* % (n/N)	ITT (all data)† % (n/N)	ITT (Worst Case)‡ % (n/N)
Lansoprazole 30 mg capsules/ clarithromycin 500 mg/ amoxicillin 1000 mg (all twice daily)	14/ M93-131	92 (44/48)	94 (47/50)	86 (47/55)
	14/ M95-392	86 (57/66)	87 (58/67)	83 (58/70)
Lansoprazole 30 mg capsules/ clarithromycin 500 mg/ amoxicillin 1000 mg (all twice daily)	10/ M95-399	84 (103/123)	86 (110/128)	81 (110/135)
Lansoprazole 30 mg capsules/ clarithromycin 250 mg/ amoxicillin 1000 mg (all twice daily)	7/ GB 94/110	90 (103/114)	90 (104/116)	86 (104/121)

Definitions: ITT = intent-to-treat patients

* Based on evaluable patients with confirmed duodenal ulcer and/or gastritis and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

† Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer.

‡ "Worst case" included patients with no available data as failures.

Patients were included in the analysis if they had documented duodenal ulcer (active) and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest®, histology and/or culture.

Pediatrics (6 to 17 years of age)

Pediatric GERD (erosive and non-erosive esophagitis)

RIVA-LANSOPRAZOLE is indicated for treatment of erosive and non-erosive GERD in children, aged 6 to 17 years. The clinical trial treatment period did not extend beyond 12 weeks.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin (Please refer to the Amoxicillin Product Monograph before prescribing).
- Clarithromycin is contraindicated in patients with known hypersensitivity to clarithromycin, erythromycin or other macrolide antibacterial agents. Clarithromycin is also contraindicated in patients receiving concurrent therapy with astemizole, terfenadine, cisapride or pimozide (please refer to the Clarithromycin tablets Product Monograph before prescribing).
- Co-administration with rilpivirine is contraindicated. See DRUG INTERACTIONS, Table 11.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

If taking lansoprazole in combination with clarithromycin, note that clarithromycin should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first 3 months of pregnancy. If pregnancy occurs while taking the drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-fetal development in monkeys, mice, rats and rabbits at doses that produced plasma levels 2 to 17 times the serum levels obtained in humans treated at the maximum recommended doses (see WARNINGS AND PRECAUTIONS section in the Clarithromycin Product Monograph).

General

Gastric Malignancy

Symptomatic response to therapy with lansoprazole delayed-release capsules does not preclude the presence of gastric malignancy.

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *Clostridium difficile* colitis.

Clostridium Difficile-Associated Diarrhea

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 can lead to an increased risk of gastrointestinal infections such as *Salmonella, Campylobacter* and *Clostridium difficile*.

An increased risk for *Clostridium difficile* infection (CDI) and *Clostridium difficile*-associated diarrhea (CDAD) has been observed in association with PPI use in several observational studies. CDI/CDAD should be considered in the differential diagnosis for diarrhea that does not improve. Additional risk factors for CDI and CDAD include recent hospitalization, the use of antibiotics, old age and the presence of co-morbidities.

Patients should be prescribed PPIs at the lowest dose and for the shortest duration required for the condition being treated and be reassessed to ascertain whether continued PPI therapy remains beneficial.

Concomitant Use with Methotrexate

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).

H. pylori Eradication and Compliance

To avoid failure of the eradication treatment with a potential for developing antimicrobial resistance and a risk of failure with subsequent therapy, patients should be instructed to follow closely the prescribed regimen.

For the eradication of *H. pylori*, amoxicillin and clarithromycin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.

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 multiple 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. See TOXICOLOGY, Mutagenicity and Carcinogenesis for further details.

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 2 months of therapy. By 1 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 DETAILED PHARMACOLOGY and TOXICOLOGY.

Drug Interactions with Antiretroviral Drugs

PPIs have been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. A change in gastric pH may change the absorption of the antiretroviral drug. Other possible mechanisms are via CYP 2Cl9.

Rilpivirine

Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS).

Atazanavir and Nelfinavir

Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir, nelfinavir exposure. (see the Atazanavir and Nelfinavir Product Monographs).

If the combination of lansoprazole with atazanavir is judged unavoidable, close clinical clinical monitoring is recommended in combination with the use of 400 mg atazanavir/100 mg ritonavir dose; the dose of lansoprazole should not exceed an equivalent dose of omeprazole of 20 mg daily. (see Atazanavir Product Monograph)."

Saquinavir

If lansoprazole is co-administered with saquinavir/ritonavir, caution and monitoring for potential saquinavir toxicities, including gastrointestinal symptoms, increased triglycerides, deep vein thrombosis and QT prolongation, are recommended. Dose reduction of saquinavir should be considered from the safety perspective for individual patients. (see Saquinavir Product Monograph).

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. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcemia and/or hypokalemia) 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.

Cyanocobalamin (Vitamin B12) Deficiency

The prolonged use of proton pump inhibitors may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of cyanocobalamin (Vitamin B12) deficiency.

Interference with Laboratory Tests

During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, lansoprazole delayed-release capsules treatment should be stopped 14 days before CgA measurements (see DRUG INTERACTIONS).

Gastrointestinal

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with lansoprazole delayed-release capsules is instituted as treatment with this drug may alleviate symptoms and delay diagnosis.

Long-term use of lansoprazole is associated with an increased risk of fundic gland polyps, especially beyond one year (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). Most fundic gland polyps are asymptomatic. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

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 1-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 DETAILED 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.

Immune

Allergic reactions (including anaphylaxis) have been reported in patients receiving clarithromycin orally.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, corticosteroids, and airway management, including intubation, as indicated.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping lansoprazole delayed-release capsules. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs (see ADVERSE REACTIONS, PostMarket Adverse Drug Reactions).

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 5 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 DETAILED PHARMACOLOGY and TOXICOLOGY.

Renal

No dosage adjustment of lansoprazole is necessary in patients with renal impairment. See DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY.

For the eradication of *H. pylori*, amoxicillin and clarithromycin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.

Sensitivity/Resistance

Antibiotic Resistance in Relation to *H. pylori* Eradication

Three patients [3/82 (3.7%)] who had isolates susceptible to clarithromycin pretreatment and were treated with the triple therapy regimen remained *H. pylori* positive post-treatment. None of the isolates from these 3 patients had susceptibility results available after treatment with triple therapy; therefore, it is unknown whether or not these patients developed resistance to clarithromycin. Sixteen percent of the patients treated with the dual therapy regimen developed clarithromycin resistance post-treatment. Therefore, development of clarithromycin resistance should be considered as a possible risk.

Use in Women

Over 4000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events are also 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), revealed no lansoprazole-related impairment of fertility, fetal malformations or developmental toxicity to fetuses or suckling neonates. Lansoprazole is not considered to be teratogenic.

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. See TOXICOLOGY, Reproduction and Teratology.

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

If taking lansoprazole in combination with clarithromycin, refer to complete Product Monograph for clarithromycin before using in pregnant women.

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

Pediatrics (6 to 17 years of age): Safety and effectiveness have been established in pediatric patients 6 to 17 years of age for short-term treatment of 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.

Developmental toxicity studies revealed that exposure to lansoprazole in juvenile rats starting at postnatal Days 7, 14, and 21 (approximately equivalent to neonatal, 1, and 2 year old human, respectively) resulted in development of heart valve thickening (see TOXICOLOGY, Juvenile Animal Toxicity Data). However, the development of heart valve thickening has not been reported in pediatric clinical trials or in post-market reports.

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).

Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also 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 2 and Table 3, respectively). Numbers in parentheses indicate the percentage of the adverse events reported.

Table 2. 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 once daily for 4 to 8 weeks.

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

placebo-treated patients; of those considered to be possibly or probably treatment-related adverse events, one or more were reported by 56/254 (22.0%).

The most frequent adverse events 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 adverse events reported in the Asian short-term studies were unspecified laboratory test abnormalities (7.3%), eosinophilia (1.0%), and increased SGPT (1.0%).

Table 3. 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 once daily for 4 to 8 weeks.

NSAID-Associated Gastric Ulcer Studies

The following tables summarize the most frequently reported treatment-emergent adverse events in the two (2) *Healing* studies and the *Reduction of Risk* study (Table 4 and Table 5, respectively).

Table 4. Most Frequently Reported* Treatment-Emergent Adverse Events by Treatment Group and Dose in the Principal Healing of NSAID-Associated Gastric Ulcer Studies†

Body System/ COSTART Term	Ranitidine 150 mg twice daily (N=235) (%) (n)	Lansoprazole 15 mg once daily (N=235) (%) (n)	Lansoprazole 30 mg once daily (N=231) (%) (n)
Total Patients			
Any Event	47% (110)	43% (102)	52% (120)
Body as a Whole			
Abdominal Pain	7% (17)	3% (7)	5% (11)
Digestive System			
Diarrhea	8% (19)	11% (25)	9% (21)
Respiratory System			
Pharyngitis	7% (16)	6% (13)	7% (17)

* Reported by ≥ 5% of patients in any treatment group
† Treatment Duration: 8 weeks

Table 5. Most Frequently Reported* Treatment-Emergent Adverse Events by Treatment Group and Dose in the Principal Reduction of Risk of NSAID-Associated Gastric Ulcer Studies†

Body System/ COSTART Term	Placebo (N = 133) % (n)	Misoprostol 200 mcg four times daily (N = 134) % (n)	Lansoprazole 15 mg once daily (N = 136) % (n)	Lansoprazole 30 mg once daily (N = 132) % (n)
Body as a Whole				
Abdominal Pain	7% (9)	10% (14)	7% (9)	6% (8)
Digestive System				
Diarrhea	7% (9)	25% (33)‡,§,¶	10% (14)	13% (17)
Nausea	5% (6)	6% (8)	1% (2)	5% (6)
Respiratory System				
Pharyngitis	3% (4)	9% (12)	7% (10)	9% (12)‡
Sinusitis	2% (3)	2% (3)	5% (7)	6% (8)
Urogenital System				
Urinary Tract Infection	2% (2)	7% (9)¶	4% (6)	1% (1)

* Reported by ≥ 5% of patients in any treatment group
† Treatment Duration: 12 weeks
‡ Statistically significant difference versus placebo ($p \leq 0.05$)
§ Statistically significant difference versus lansoprazole 15 mg once daily ($p \leq 0.05$)
¶ Statistically significant difference versus lansoprazole 30 mg once daily ($p \leq 0.05$)

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 6.

Table 6. Adverse Events Possibly/Probably Related to Treatment, Reported by ≥ 5% of Patients in the U.S. Placebo-Controlled Non-Erosive GERD Studies

Body System/ COSTART term	Placebo	Lansoprazole*
	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 once daily 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 treatment are displayed by body system, COSTART term, and treatment in Table 7.

Table 7. Most Frequently* Reported Possibly/Probably Treatment-Related Adverse Events by Treatment in the Positive-Controlled Non-Erosive GERD Studies

Body System/COSTART term	Ranitidine 150 mg twice daily (N=283) % (n)	Lansoprazole † 15 and 30 mg once daily (N=572) % (n)
Total Patients Any event	17 (49)	16 (91)
Body as a Whole		
Abdominal Pain	2 (5)	5 (29) ‡
Digestive System		
Diarrhea	6 (18)	4 (23)

* Reported by ≥ 5% of patients in any treatment.
† Statistically significantly different versus ranitidine at p = 0.05 level.
‡ Doses 15 mg and 30 mg once daily 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 adverse events 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 8.

There were no frequently reported (≥ 2.0%, incidence) severe adverse events 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 8. Treatment-Emergent Adverse Events Reported by ≥ 2% of the Placebo and Lansoprazole Patients to the Time of First Recurrence of Disease* in the Maintenance Treatment Studies

Mean Exposure (Days)	Placebo Cumulative N=236 (105.4)	Lansoprazole Cumulative N=386 (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)
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

<u>European Studies</u>

The adverse events 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 9.

Table 9. Treatment-Emergent Adverse Events Reported by ≥ 2% of Patients Treated with Histamine H2-Receptor Antagonists or Lansoprazole in Long-Term, Phase II/III Histamine H2-Receptor Antagonist Controlled European Studies

Body System/COSTART term	Lansoprazole (N=263) % (n)	Histamine H2-Receptor Antagonists (N=161) % (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		
Respiratory Disorder	2.3 (6)	3.1 (5)
Cough increased	1.1 (3)	2.5 (4)

The adverse events 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 adverse events 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 Histamine H2-Receptor Antagonist 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 to 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 non-erosive 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; see (Post-Market Adverse Drug Reactions).

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), syncope, tachycardia, vasodilation;

Digestive System: Abnormal stools, anorexia, bezoar, carcinoid, cardiospasm, cholelithiasis, colitis, constipation, dry mouth, 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, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis;

Endocrine System: Diabetes mellitus, goiter, hypothyroidism;

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

Metabolism and Nutritional Disorders: Dehydration, gout, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss;

Musculoskeletal System: Arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis;

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased, libido increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, 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, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urination impaired, urinary urgency, vaginitis.

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

Combination Therapy with Clarithromycin and Amoxicillin

In clinical trials using combination therapy with lansoprazole delayed-release capsules plus clarithromycin and amoxicillin, and lansoprazole delayed-release capsules plus amoxicillin, no adverse reactions related to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that have been previously reported with lansoprazole delayed-release capsules, clarithromycin, or amoxicillin.

For more information on adverse reactions with clarithromycin or amoxicillin, refer to their respective Product Monographs, under the ADVERSE REACTIONS section.

Triple Therapy: lansoprazole/clarithromycin/amoxicillin

The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). Patients in the 7-day triple therapy regimen reported fewer adverse events than those in the 10 and/or 14-day triple therapy regimens. There were no statistically significant differences in the frequency of reported adverse events between the 10 and 14-day triple therapy regimens.

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 white blood cells (WBC), abnormal AG ratio, abnormal red blood cells (RBC), bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased lactate dehydrogenase (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) and 0.4% (11/2677) patients, who received placebo and lansoprazole, respectively, had enzyme elevations > 3 x upper limit of normal range at the final treatment visit. None of these lansoprazole-treated patients reported jaundice at any time during the study.

For more information on laboratory value changes with clarithromycin or amoxicillin, refer to their respective Product Monographs, under the ADVERSE REACTIONS section.

Post-Market Adverse Drug Reactions

These events were reported during post-marketing 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;
Hemic and Lymphatic System:	agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura;
Metabolism and Nutritional Disorders:	hypomagnesemia, hypocalcemia* and hypokalemia*;
Musculoskeletal System:	myositis, osteoporosis and osteoporosis-related fractures;
Skin and Appendages:	severe dermatologic reactions including cutaneous lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal), DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) (some fatal);
Special Senses:	speech disorder;
Urogenital System:	interstitial nephritis (with possible progression to renal failure), urinary retention.

* May be related to the occurrence of hypomagnesemia

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 2 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 2 of these 10 cases, 1 of the examining ophthalmologists proposed a diagnosis of anterior ischemic optic neuropathy (AION). Eight out of the 10 cases were foreign-sourced. Only 2 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.

There have been post-marketing reports of subacute cutaneous lupus erythematosus (SCLE) (See WARNINGS AND PRECAUTIONS, Immune).

There have been post-marketing reports of fundic gland polyps (FGPs) (see WARNINGS AND PRECAUTIONS, Gastrointestinal).

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, 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.

Drugs that Inhibit or Induce CYP2C19

Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure to lansoprazole. Inducers of CYP2C19 may decrease the systemic exposure to lansoprazole.

Drugs with pH Dependent Absorption Pharmacokinetics

Lansoprazole causes a profound and long lasting inhibition of gastric acid secretion; therefore, 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

Table 10. Established or Potential Drug-Drug Interactions with Lansoprazole

Concomitant Drug Name	Ref	Effect	Clinical Comment
Antiretroviral Drugs	C	↓ rilpivirine, atazanavir, nelfinavir ↑saquinavir	*Rilpivirine* Co-administration is contraindicated due to significant decreases in rilpivirine exposure and loss of therapeutic effect (see CONTRAINDICATIONS). *Atazanavir* Co-administration of lansoprazole with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma C_{max} and AUC of atazanavir in healthy

Concomitant Drug Name	Ref	Effect	Clinical Comment
			volunteers administered atazanavir or atazanavir/ritonavir. (see Atazanavir Product Monograph). Nelfinavir Co-administration of lansoprazole with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and C_{max} for nelfinavir (by 36% and 37%, respectively) and its active metabolite M8 (by 92% and 89%, respectively). (see Nelfinavir Product Monograph). *Saquinavir* Co-administration of saquinavir requires caution and monitoring, along with potential dose reduction of saquinavir, due to increased saquinavir exposure and thus the risk of saquinavir-related toxicities. (see the Saquinavir Product Monograph). Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1000/100 mg twice daily) increased saquinavir AUC by 82% and C_{max} by 75%.
Clopidogrel	CT	-	Concomitant administration of lansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of lansoprazole.
CYP450			
Methotrexate	C, CT	-	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, possibly leading to methotrexate toxicities. 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 lansoprazole 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.
Sucralfate	CT	Lansoprazole: AUC ↓, C_{max} ↓	Proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered with lansoprazole and there was no evidence of a change in the efficacy of lansoprazole (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption, Absorption with Antacids).
Tacrolimus	C	Increased whole blood levels	Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Concomitant Drug Name	Ref	Effect	Clinical Comment
Theophylline (CYP1A2, CYP3A)	CT	10% increase in theophylline clearance	Minor increase of theophylline clearance is unlikely to be of clinical concern. Individual patients may require adjustment of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels. Patient monitoring should be taken in coadministration of lansoprazole with theophylline.
Warfarin	C, CT	↑ INR and PT	In a study of healthy subjects, neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following co-administration of single or multiple 60 mg doses of lansoprazole and warfarin; however, there have been reports of increased 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.

Legend: C = Case Study; CT = Clinical Trial, T = Theoretical

Combination Therapy with Clarithromycin and/or Amoxicillin

For more information on drug interactions for clarithromycin and amoxicillin, refer to their respective Product Monographs, under DRUG INTERACTIONS.

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. Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, lansoprazole delayed-release capsules treatment should be stopped 14 days before CgA measurements (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Pharmacodynamic Properties).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Duodenal Ulcer

Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy: RIVA-LANSOPRAZOLE/clarithromycin/amoxicillin

For the eradication of *H. pylori*, amoxicillin and clarithromycin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.

Gastric Ulcer

RIVA-LANSOPRAZOLE (lansoprazole delayed-release capsules) is not indicated for maintenance therapy in the treatment of patients with gastric ulcer.

Recommended Dose and Dosage Adjustment

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Duodenal Ulcer

The recommended adult oral dose is 15 mg once daily before breakfast for 2 to 4 weeks (see INDICATIONS AND CLINICAL USE).

A small percentage of patients who are *H. pylori* negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. RIVA-LANSOPRAZOLE 15 mg once daily before breakfast may be used up to 1 year for the maintenance treatment of recurrent duodenal ulcers.

***Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

Triple Therapy: RIVA-LANSOPRAZOLE/clarithromycin/amoxicillin

The recommended adult oral dose is 30 mg lansoprazole, 500 mg clarithromycin, and 1000 mg amoxicillin, all given twice daily for 7, 10 or 14 days (see INDICATIONS AND CLINICAL USE). Daily doses should be taken before meals.

(FOR ADDITIONAL INFORMATION ON TRIPLE THERAPY FOR THE TREATMENT OF *H. PYLORI* INFECTION AND ACTIVE DUODENAL ULCER RECURRENCE, REFER TO THE HP-PAC PRODUCT MONOGRAPH.)

Gastric Ulcer

The recommended adult oral dose is 15 mg once daily before breakfast for 4 to 8 weeks.
No dosage adjustment is necessary in patients with renal impairment. No dosage adjustment is necessary in the initial RIVA-LANSOPRAZOLE dosing regimen for older patients and for patients with mild to moderate hepatic impairment. Dosing recommendations described in the labelling should be adhered to for older patients and patients with hepatic impairment.

NSAID-Associated Gastric Ulcer

The issue of whether or not eradication of *H. pylori* in patients with NSAID-associated ulcers might have beneficial effects remains unresolved (Chan et al, 2001).

Healing of NSAID-Associated Gastric Ulcer

The recommended adult oral dose is 15 to 30 mg once daily before breakfast for up to 8 weeks. A trend for higher healing rates (4% and 12%, two studies) was observed with the 30 mg dose, as compared to the 15 mg dose (see CLINICAL TRIALS).

Reduction of Risk of NSAID-Associated Gastric Ulcer
The recommended adult oral dose is 15 mg once daily before breakfast for up to 12 weeks (see CLINICAL TRIALS).

Reflux Esophagitis or Poorly Responsive Reflux Esophagitis Including Patients with Barrett's Esophagus
The recommended adult oral dose is 30 mg once daily before breakfast for 4 to 8 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 (see CLINICAL TRIALS).

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

Treatment and Maintenance of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of RIVA-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 twice daily 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 4 years (see 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 once 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)
In clinical studies, lansoprazole was not administered beyond 12 weeks in 6 to 11 year olds. It is not known if lansoprazole is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in children as outlined below.

Children 6 to 11 years of age
The recommended pediatric oral dose for children 6 to 11 years of age is 15 mg (≤ 30 kg) and 30 mg (>30 kg) once daily for up to 12 weeks.

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 RIVA-LANSOPRAZOLE should not exceed 30 mg (see WARNINGS AND PRECAUTIONS).

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

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

Missed Dose

Patients should be instructed that if a dose of this medication has been missed, it should be taken as soon as possible. However, if the next scheduled dose is due, the patient should not take the missed dose, and should be instructed to take the next dose on time. Patients should be instructed not to take 2 doses at one time to make up for a missed dose.

Administration

RIVA-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. RIVA-LANSOPRAZOLE capsules SHOULD NOT BE CRUSHED, CHEWED, BROKEN OR CUT.

Concomitant Antacid Use
Simultaneous administration of RIVA-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, RIVA-LANSOPRAZOLE should be administered at least 30 minutes prior to sucralfate (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption, 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.

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 among Duodenal Ulcer and hypersecretory patients, and basal gastric acid secretion among patients with Gastric Ulcer disease.

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.

Pharmacodynamic Properties

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued 14 days prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range (see WARNINGS AND PRECAUTIONS, Interference with Laboratory Tests).

Eradication of Helicobacter pylori

Helicobacter pylori is considered to be a major factor in the etiology of duodenal ulcer disease. The presence of *H. pylori* may damage the mucosal integrity due to the production of enzymes (catalase, lipases, phospholipases, proteases, and urease), adhesins and toxins; the inflammatory response generated in this manner contributes to mucosal damage.

The concomitant administration of an antimicrobial(s) and an antisecretory agent such as lansoprazole, improves the eradication of *H. pylori* as compared to individual drug administration. The higher pH resulting from antisecretory treatment, optimizes the environment for the pharmacologic action of the antimicrobial agent(s) against *H. pylori*.

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 11 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 DETAILED PHARMACOLOGY, Animal.

Table 11. 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 (3 hours after a meal) indicated that both C_{max} and AUC values were increased by approximately 2-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 1 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. Lansoprazole is thought to be transformed into 2 active species that inhibit acid secretion by blocking the proton pump (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. The 2 active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

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.

Following a 30 mg single intravenous dose of lansoprazole, the mean clearance was 11.1 (± 3.8) L/h.

Special Populations and Conditions

Pediatrics (1 to 17 years of age): 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 once daily for subjects weighing ≤ 30 kg and 30 mg once daily for subjects weighing > 30 kg. The pharmacokinetics were also studied in adolescents aged 12 to 17 years with GERD following 15 mg or 30 mg once daily of lansoprazole.

Pharmacokinetic parameters for lansoprazole following 15 or 30 mg once daily 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 12.

Table 12. 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 *	30 mg *	15 mg	30 mg	30 mg †
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) ‡	0.68 ± 0.21	0.71 ± 0.22	0.84 ± 0.26	0.95 ± 0.31	1.19 ± 0.52

* 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.
† Data obtained from healthy adult subjects normalized to a 30 mg dose.
‡ 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 once daily 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 WARNINGS AND 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 Impairment: 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 Impairment: 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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

RIVA-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 two dosage strengths: 15 mg and 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 (30 mg capsules only), FD&C green No. 3 (15 mg capsules only), FD&C red No. 3, gelatin, hydroxypropyl cellulose, hypromellose, macrogol, maize starch, magnesium carbonate, methacrylic acid-ethyl acrylate copolymer, polysorbate 80, silica colloidal anhydrous, sucrose, sugar spheres, talc, titanium dioxide.

Dosage Forms and Packaging

RIVA-LANSOPRAZOLE is available as 15 mg, pink cap-green body capsules imprinted with "15" in white ink on the body and containing white to off white pellets. The capsules are available in bottles of 100.

RIVA-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 and 500.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

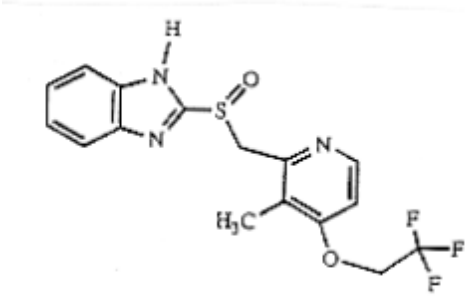
Proper Name: Lansoprazole

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 RIVA-LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Laboratoire Riva Inc.) 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)		

* RIVA-LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Laboratoire Riva Inc.)

† 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 RIVA-LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Laboratoire Riva Inc.) 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)		

* RIVA-LANSOPRAZOLE (lansoprazole) 30 mg delayed-release capsules (Laboratoire Riva Inc.).
† 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

Duodenal Ulcer

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, and 60 mg of lansoprazole delayed-release capsules once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after 2 and 4 weeks was significantly higher with all doses of lansoprazole delayed-release capsules than with placebo (Table 13). There was no evidence of a greater or earlier response with the two higher doses compared with lansoprazole delayed-release 15 mg. Based on this study and the second study described below, the recommended dose of lansoprazole delayed-release in duodenal ulcer is 15 mg/day.

Table 13. Duodenal Ulcer Healing Rates

Week	Lansoprazole 15 mg once daily (N = 68)	Lansoprazole 30 mg once daily (N = 74)	Lansoprazole 60 mg once daily (N = 70)	Placebo (N = 72)
2	42.4%*	35.6%*	39.1%*	11.3%
4	89.4%*	91.7%*	89.9%*	46.1%

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

Lansoprazole delayed-release capsules 15 mg were significantly more effective than placebo in relieving day and nighttime abdominal pain and in decreasing the amount of antacid taken per day.

In a second U.S. multicenter study, also double-blind, placebo-, dose-comparison (15 and 30 mg lansoprazole delayed-release capsules once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after 4 weeks was significantly higher with both doses of lansoprazole delayed-release than with placebo (Table 14). There was no evidence of a greater or earlier response with the higher dose of lansoprazole delayed-release. The 15 mg dose of lansoprazole delayed-release was superior to ranitidine at 4 weeks. No significant difference was seen between treatment groups at 2 weeks. In addition, no difference between lansoprazole delayed-release and ranitidine was noted at 4 weeks.

Table 14. Duodenal Ulcer Healing Rates

Week	Lansoprazole 15 mg once daily (N = 80)	Lansoprazole 30 mg once daily (N = 77)	Ranitidine 300 mg at bedtime (N = 82)	Placebo (N = 41)
2	35.0%	44.2%	30.5%	34.2%
4	92.3%*	80.3%†	70.5%†	47.5%

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

Helicobacter pylori **Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

Randomized, double-blind clinical studies in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within 1 year) evaluated the efficacy of lansoprazole delayed-release capsules in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or in combination with amoxicillin as dual 14-day therapy for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy:	lansoprazole delayed-release capsules 30 mg twice daily/clarithromycin 500 mg twice daily / amoxicillin 1000 mg twice daily
Dual therapy:	lansoprazole delayed-release capsules 30 mg three times daily / amoxicillin 1000 mg three times daily

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

Triple therapy was shown to be more effective than all possible dual therapy combinations (Table 15). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within 1 year) compared the efficacy of lansoprazole delayed-release capsules triple therapy for 10 and 14 days. This study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori* (Table 15**)**.

Table 15. *H. pylori* Eradication Rates - Triple Therapy (lansoprazole/clarithromycin/amoxicillin) Percent of Patients Cured [95% Confidence Interval] (Number of Patients)

Study	Duration	Triple Therapy Evaluable Analysis*	Triple Therapy Intent-to-Treat Analysis†
#1 (M93-131)	14 days	92‡ [80.0-97.7] (N=48)	86‡ [73.3-93.5] (N=55)
#2 (M95-392)	14 days	86§ [75.7-93.6] (N=66)	83§ [72.0-90.8] (N=70)
#3 (M95-399)¶	14 days	85 [77.0-91.0] (N=113)	82 [73.9-88.1] (N=126)
	10 days	84 [76.0-89.8] (N=123)	81 [73.9-87.6] (N=135)

* Based on evaluable patients with confirmed duodenal ulcer (active or within 1 year) and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest® (Delta West Ltd., Bentley, Australia), histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

† Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within 1 year). All dropouts were included as failures of therapy.
‡ ($p < 0.05$) versus lansoprazole/amoxicillin and lansoprazole/clarithromycin dual therapy.
§ ($p < 0.05$) versus clarithromycin/amoxicillin dual therapy.
¶ The 95% confidence interval for the difference in eradication rates, 10-day minus 14-days is (-10.5, 8.1) in the evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.

A randomized, open-label, parallel-group, multicenter clinical study performed in the U.K. in patients with *H. pylori* and duodenal ulcer disease and/or gastritis, compared the efficacy and safety of four 7-day triple therapy treatment regimens. The primary efficacy measure was eradication of *H. pylori* as defined by a negative ^{13}C-urea breath test at least 28 days (Visit 3) after completing study medication. This study established that 7-day triple therapy with lansoprazole/clarithromycin/amoxicillin was as clinically effective in eradication *H. pylori* as the 10- or 14-day treatment regimens (Table 16).

Table 16. Post-treatment Breath Test Results by Patient Population *H. pylori* Eradication Rates - Triple Therapy Regimen (lansoprazole/clarithromycin/amoxicillin)

Population Study #4 (GB 94/110)	Lansoprazole 30 mg twice daily + clarithromycin 250 mg twice daily + amoxicillin 1000 mg twice daily
Evaluable (Per Protocol)*	
Positive n (%)	11 (9.6)
Negative n (%)	103 (90.4)
95% CI (eradication rate)	83.0, 94.8
Intent-to-treat#	
Positive n (%)	12 (10.3)
Negative n (%)	104 (89.7)
95% CI (eradication rate)	82.3, 94.3
Intent-to-treat (Worst case) †	
Positive n (%)	17 (14.0)
Negative n (%)	104 (86.0)
95% CI (eradication rate)	78.2, 91.4
Intent-to-treat (Best case)†	
Positive n (%)	12 (9.9)
Negative n (%)	109 (90.1)
95% CI (eradication rate)	83.0, 94.5

* Based on evaluable patients with confirmed duodenal ulcer and /or gastritis and *H. pylori* infection at baseline defined as at least 2 of 3 positive endoscopic tests from CLOtest®, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.
† "Worst case" assumed that missing Visit 3 breath test results were positive for *H. pylori* and "Best case" results assumed that missing Visit 3 results were negative for *H. pylori*.
\# Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer.

A combination of lansoprazole plus clarithromycin and amoxicillin as triple therapy, was effective in eradicating *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

There were no statistically significant differences in *H. pylori* eradication rates between the levels of any potentially influential factors, including baseline duodenal ulcer status, baseline duodenal ulcer size, gender, age, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses. *H. pylori* eradication rates at the Week 6 Visit for patients who received lansoprazole delayed-release capsules 30 mg twice daily, clarithromycin 500 mg twice daily, and amoxicillin 1000 mg twice daily are presented by concomitant factors in Table 17 and Table 18 for the 14-day and 10-day treatment studies, respectively.

A statistically significant difference in ulcer prevalence rates was observed between the levels for age in the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses, with younger patients demonstrating a lower ulcer prevalence rate compared with older patients. No statistically significant differences in ulcer prevalence rates were observed between the levels of other potentially influential factors including baseline duodenal ulcer status, baseline duodenal ulcer size, gender, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

A statistically significant difference in *H. pylori* eradication rates was observed between the levels of baseline duodenal ulcer size in the evaluable and intent-to-treat (all available data) analyses, with patients who had smaller ulcers (3 to 5 mm) demonstrating a lower *H. pylori* eradication rate compared with patients who had larger ulcers. Statistically significant differences in *H. pylori* eradication rates were also observed between the levels of age in the intent-to-treat (all available data) and modified intent-to-treat (worst case) analyses, with patients over 65 years of age demonstrating a higher *H. pylori* eradication rate compared with patients less than or equal to 65 years of age. No statistically significant differences in *H. pylori* eradication rates were observed between the levels of other potentially influential factors including baseline duodenal ulcer status, gender, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

Table 17. *H. pylori* Eradication Rates at the Week 6 Visit for Patients Who Received 14 days of Lansoprazole 30 mg Twice Daily, Clarithromycin 500 mg Twice Daily, and Amoxicillin 1000 mg Twice Daily by Concomitant Factors

Factor	% (n/N)		
	Evaluable	Intent-to-Treat (All Available Data)	Modified Intent-to-Treat (Worst Case)
Baseline Duodenal Ulcer Status			
Active	88% (88/100)	89% (91/102)	83% (91/110)
Historical	93% (13/14)	93% (14/15)	93% (14/15)
Baseline Duodenal Ulcer Size			
3 to 5 mm	85% (23/27)	86% (24/28)	83% (24/29)
> 5 to 10 mm	89% (55/62)	92% (57/62)	84% (57/68)
> 10 mm	91% (10/11)	83% (10/12)	77% (10/13)
Gender			
Female	89% (31/35)	89% (32/36)	84% (32/38)
Male	89% (70/79)	90% (73/81)	84% (73/87)
Age			
< 45	87% (46/53)	88% (50/57)	83% (50/60)
45 to 65	92% (43/47)	92% (43/47)	84% (43/51)
> 65	86% (12/14)	92% (12/13)	86% (12/14)

Factor	% (n/N)		
	Evaluable	Intent-to-Treat (All Available Data)	Modified Intent-to-Treat (Worst Case)
Race			
Black	82% (22/27)	82% (23/28)	79% (23/29)
Caucasian	92% (57/62)	91% (59/65)	83% (59/71)
Other	88% (22/25)	96% (23/24)	92% (23/25)
Tobacco Use			
Nonuser*	89% (56/63)	92% (58/63)	87% (58/67)
User	88% (45/51)	87% (47/54)	81% (47/58)

No statistically significant differences were observed between the levels of any factor after stratification by study.
* Includes ex-tobacco users

Table 18. *H. pylori* Eradication Rates at the Week 6 Visit for Patients Who Received 10 days of Lansoprazole 30 mg Twice Daily, Clarithromycin 500 mg Twice Daily, and Amoxicillin 1000 mg Twice Daily by Concomitant Factors

Factor	% (n/N)		
	Evaluable	Intent-to-Treat (All Available Data)	Modified Intent-to-Treat (Worst Case)
Baseline Duodenal Ulcer Status			
Active	86% (91/106)	88% (97/110)	83% (97/117)
Historical	71% (12/17)	72% (13/18)	72% (13/18)
Baseline Duodenal Ulcer Size*			
3 to 5 mm	77% (34/44)	80% (36/45)	75% (36/48)
> 5 to 10 mm	91% (43/47)	94% (47/50)	82% (47/52)
> 10 mm	93% (14/15)	93% (14/15)	82% (14/17)
Gender			
Female	79% (38/48)	82% (42/51)	79% (42/53)
Male	87% (65/75)	88% (68/77)	83% (68/82)
Age			
< 45	85% (33/39)	85% (35/41)	80% (35/44)
45 to 65	82% (56/68)	86% (61/71)	81% (61/75)
> 65	88% (14/16)	88% (14/16)	88% (14/16)
Race			
Black	84% (16/19)	90% (18/20)	78% (18/23)
Caucasian	82% (62/76)	83% (66/80)	80% (66/82)
Other	89% (25/28)	93% (26/28)	87% (26/30)
Tobacco Use			
Nonuser†	83% (59/71)	87% (65/75)	81% (65/80)
User	85% (44/52)	85% (45/53)	82% (45/55)

No statistically significant differences were observed among the levels of any factor.
* Includes only patients with active duodenal ulcer at baseline
† Includes ex-tobacco users

A statistically significant difference in ulcer prevalence rates was observed between baseline duodenal ulcer status (active or historical) in the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses, with patients who had a historical duodenal ulcer at baseline demonstrating a lower ulcer prevalence rate compared with patients who had an active duodenal ulcer at baseline. No statistically significant differences in ulcer prevalence rates were observed among the levels of other potentially influential factors including baseline duodenal ulcer size, gender, age, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

Gastric Ulcer

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, and 60 mg of lansoprazole delayed-release capsules once daily) study of 253‡ patients with an endoscopically documented, single, acute gastric ulcer, defined as a lesion with depth that had a crater size of at least 3 mm in diameter, the percentage of patients healed at 4 and 8 weeks was significantly higher with lansoprazole delayed-release capsules 15 and 30 mg once a day than with placebo (Table 19):

‡ Number of patients who were included in at least one of the primary efficacy analyses.

Table 19. Gastric Ulcer Healing Rates

Week	Lansoprazole 15 mg once daily (N = 65)	Lansoprazole 30 mg once daily (N = 63)	Lansoprazole 60 mg once daily (N = 61)	Placebo (N = 64)
4	64.6%* (42/65)	58.1%* (36/62)	53.3% (32/60)	37.5% (24/64)
6	87.5%* (56/64)	75.4% (46/61)	78.3%* (47/60)	59.0% (36/61)
8	92.2%* (59/64)	96.8%* (60/62)	93.2%* (55/59)	76.7% (46/60)

* Statistically significantly greater healing rate ($p \leq 0.05$) than placebo using Cochran-Mantel-Haenszel methodology with investigator as stratification factor.

In this study, all lansoprazole delayed-release capsules groups reported significantly higher healing rates when compared to placebo at Week 8. At Week 4, both lansoprazole delayed-release capsules 15 and 30 mg groups had significantly higher healing rates than the placebo group. The healing rate for the 60 mg group was numerically higher than for placebo at Week 4 with the difference for the evaluable patients analysis approaching significance (p=0.054).

Lansoprazole delayed-release capsules were also compared in a U.K. multicenter, double-blind, active controlled, fixed dose (30 and 60 mg of lansoprazole delayed-release capsules, administered once daily to ranitidine 300 mg at bedtime) study of 234‡ patients with one or more endoscopically documented gastric ulcers with size between and including 3 and 25 mm in diameter. The percentage of healing rates is presented in Table 20.

‡ Number of patients who were included in at least one of the primary efficacy analyses.

Table 20. Gastric Ulcer Healing Rates

Week	Ranitidine 300 mg at bedtime (N = 79)	Lansoprazole 30 mg once daily (N = 77)	Lansoprazole 60 mg once daily (N = 78)
4	61.0% (44/77)	80.6%* (58/72)	83.3%* (60/72)
8	93.2% (68/73)	98.7% (76/77)	98.7%* (73/74)

* Statistically significantly superior to ranitidine ($p \leq 0.05$), using Cochran-Mantel-Haenszel methodology with investigator as the stratification factor.

At Week 4, both lansoprazole delayed-release capsules doses had significantly higher healing rates than ranitidine. At Week 8, the healing rates were higher in the lansoprazole groups, although the difference was statistically significant only for the lansoprazole 60 mg group in the evaluable patient analysis.

Healing of Non-Steroidal Anti-Inflammatory Drug (NSAID)-Associated Gastric Ulcer

In two U.S. and Canadian multicenter, double-blind, ranitidine-controlled studies in patients with endoscopically confirmed NSAID-associated gastric ulcer who continued their NSAID use, the percentage of patients healed after 8 weeks was statistically significantly higher with 15 or 30 mg of Lansoprazole delayed-release capsules than with ranitidine. A total of 711 patients were enrolled in the two studies, and 701 patients were treated. Patients ranged in age from 18 to 88 years (median age 59 years), with 67% female patients and 33% male patients. Race was distributed as follows: 87% Caucasian, 8% Black, 5% other. Among patients with *H. pylori* status during screening period, 27% of patients were positive and 73% of patients were negative. Gastric ulcer healing rates are summarized in Table 21.

Table 21. Gastric Ulcer* Healing Rates in Evaluable Patients

Study	Drug	N	Week 4†	N	Week 8†
#1	Ranitidine 150 mg twice daily	106	31%	92	57%
	Lansoprazole 15 mg once daily	106	48%‡	97	73%‡
	Lansoprazole 30 mg once daily	108	58%‡	96	75%‡
#2	Ranitidine 150 mg twice daily	101	37%	90	49%
	Lansoprazole 15 mg once daily	95	46%	85	73%‡
	Lansoprazole 30 mg once daily	100	50%	91	79%‡

* An ulcer was defined as a discrete lesion with appreciable depth and ≥ 5 mm in diameter.
† Patients without endoscopy were not included in the analysis.
‡ ($p \leq 0.05$) versus ranitidine

Symptom relief results for these two studies are summarized in Table 22.

Table 22. Symptom Relief During 8-Week Treatment Period-Evaluable Patients

Variable	Ranitidine 150 mg twice daily	Lansoprazole 15 mg once daily	Lansoprazole 30 mg once daily
Study #1			
Daytime Abdominal Pain			
% of Days with Pain	37.6	30.1*	33.6
Average Pain Severity/Day	0.58	0.44*	0.47
Night Abdominal Pain			
% of Nights with Pain	32.5	28.3	29.0
Average Pain Severity/Night	0.49	0.41	0.42
Study #2			
Daytime Abdominal Pain			
% of Days with Pain	46.8	33.4*	39.2
Average Pain Severity/Day	0.68	0.45*	0.55
Night Abdominal Pain			
% of Nights with Pain	42.4	30.4*	33.5
Average Pain Severity/Night	0.60	0.41*	0.46*

Severity of pain: none = 0; mild = 1; moderate = 2; and severe = 3.

* Statistically significant difference versus the ranitidine treatment group ($p \leq 0.05$).

Reduction of Risk of NSAID-Associated Gastric Ulcer

In one large U.S., multicenter, double-blind (misoprostol blinded only to endoscopist), placebo- and misoprostol-controlled study in patients who required chronic use of an NSAID and who had an endoscopically documented history of gastric ulcer, the percentage of patients remaining free from gastric ulcer after 4, 8, and 12 weeks was statistically significantly higher with 15 or 30 mg lansoprazole delayed-release capsules than with placebo. A total of 537 patients were enrolled in the study, and 535 patients were treated. Patients ranged in age from 23 to 89 years (median age 60 years), with 65% female patients and 35% male patients. Race was distributed as follows: 90% Caucasian, 6% Black, 4% other. In addition, patients were *H. pylori* negative. Patients receiving lansoprazole delayed-release capsules 15 or 30 mg remained free from gastric ulcer for a significantly longer period of time than did patients receiving placebo. No further benefit was observed with the 30 mg dose. The issue of whether or not eradication of *H. pylori* in patients with NSAID-associated ulcers might have beneficial effects remains unresolved (Chan et al, 2001).

NSAID-associated gastric ulcer risk reduction rates are summarized in Table 23.

Table 23. NSAID-Associated Gastric Ulcer Risk Reduction Rates in Evaluable Patients (% of Patients Remaining Gastric Ulcer Free)

Week	Placebo (N = 112)	Misoprostol*, †, ‡ 200 mcg four times daily (N = 106)	Lansoprazole‡ 15 mg once daily (N = 121)	Lansoprazole‡ 30 mg once daily (N = 116)
4	66%	96%	90%	92%
8	60%	95%	86%	88%
12	51%	93%	80%	82%

% = Life Table Estimate
* ($p \leq 0.05$) versus lansoprazole 15 mg
† ($p \leq 0.05$) versus lansoprazole 30 mg
‡ ($p \leq 0.001$) versus placebo

Symptom relief results for this study are summarized in Table 24.

Table 24. Symptom Relief for the 12-Week Double-Blind Treatment Period in Evaluable Patients

Variable	Placebo (N = 113)	Misoprostol 200 mcg four times daily (N = 108)	Lansoprazole 15 mg once daily (N = 126)	Lansoprazole 30 mg once daily (N = 119)
Daytime Abdominal Pain				
% of Days with Pain	34.5	41.0	27.5*	30.8*
Average Pain Severity/Day	0.51	0.60	0.39*	0.46*
Nighttime Abdominal Pain				
% of Nights with Pain	30.4	32.7	22.2*	27.1
Average Pain Severity/Night	0.45	0.49	0.32*	0.41

Severity of pain: none = 0; mild = 1; moderate = 2; and severe = 3
* Statistically significant difference versus misoprostol treatment group ($p \leq 0.05$).

Symptomatic Gastroesophageal Reflux Disease (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 25.

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

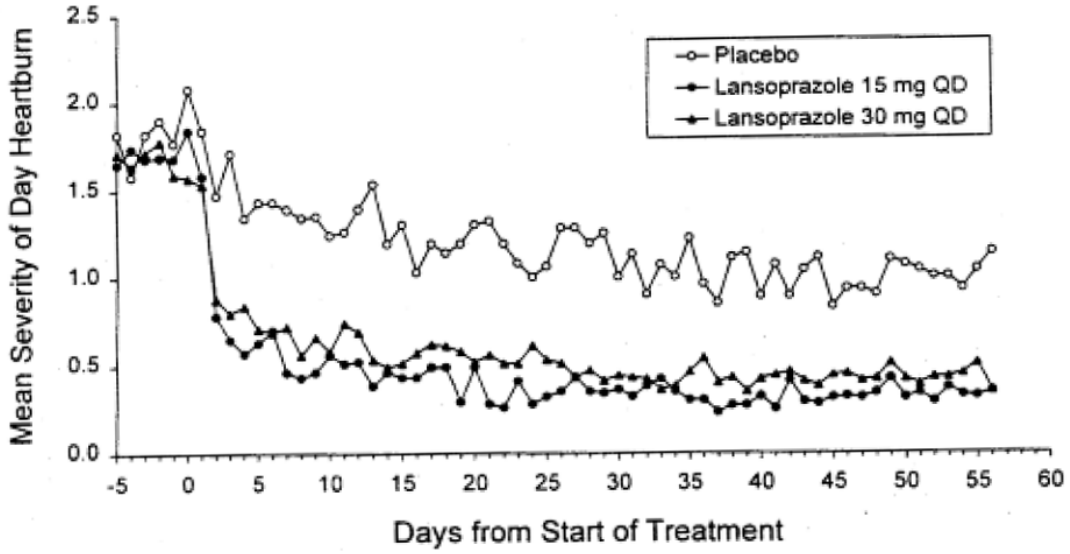


Figure 2: Mean Severity of Night Heartburn by Study Day for Evaluable Non-Erosive GERD Patients (3=Severe, 2=Moderate, 1=Mild, 0=None). Study M95-300

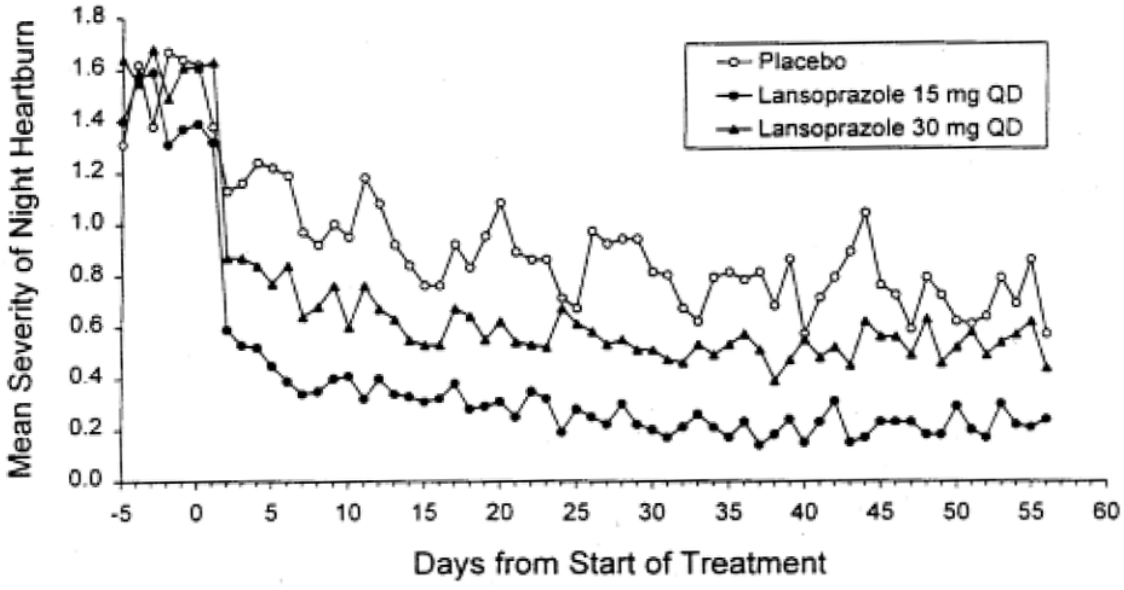


Table 25. Frequency of Heartburn at Week 1, Week 4, and Week 8 in Non-Erosive GERD Patients (Intent-to-Treat)

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 (twice daily) in decreasing the frequency and severity of day and night heartburn associated with GERD for the 8 week treatment period. No significant additional benefit from lansoprazole 30 mg once daily was observed.

‡ 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 26.

Table 26. Reflux Esophagitis Healing Rates

Week	Lansoprazole 15 mg once daily (N=69)	Lansoprazole 30 mg once daily (N=65)	Lansoprazole 60 mg once daily (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%

* ($p \leq 0.001$) versus placebo.
† ($p \leq 0.05$) 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 once daily 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 twice daily as shown in Table 27.

Table 27. Reflux Esophagitis Healing Rates

Week	Lansoprazole 30 mg once daily (N=115)	Ranitidine 150 mg twice daily (N=127)
2	66.7%*	38.7%
4	82.5%*	52.0%
6	93.0%*	67.8%
8	92.1%*	69.9%

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

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

In the two trials described and in several smaller studies involving patients with moderate to severe erosive 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 twice daily in 151 patients with erosive reflux esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least one H_2-receptor antagonist given at the dose indicated for symptom relief or greater, namely cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidine 300 mg/day. Lansoprazole delayed-release capsules 30 mg were more effective than ranitidine 150 mg twice daily in healing reflux esophagitis and the percentage of patients with healing are presented in Table 28.

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 28. Reflux Esophagitis Healing Rates in Patients Poorly Responsive to Histamine H2-Receptor Antagonist Therapy

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

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

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 non-erosive 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 once daily if ≤ 30 kg or lansoprazole 30 mg once daily if >30 kg administered for 8 to 12 weeks. The lansoprazole dose was increased (up to 30 mg twice daily) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. 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 29).

Table 29. Improvement in Overall GERD Symptoms (1 to 11 years)

GERD	Final Visit * % (n/N)
Symptomatic GERD Improvement in Overall GERD Symptoms †	76% (47/62‡)
Erosive Esophagitis Improvement in Overall GERD Symptoms † Healing Rate	81% (22/27) 100% (27/27)

* At Week 8 or Week 12
† Symptoms assessed by patients diary kept by caregiver
‡ 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 once daily or lansoprazole 30 mg once daily 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 peak plasma concentration (C_{max}) and area under the plasma concentration curve (AUC_{0-24}) of lansoprazole increased proportionately with dose from 15 to 30 mg for oral administration once daily for 5 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 once daily regimen significantly increased the percentage of time the intragastric pH was above 5.

Subjects in both the lansoprazole 15 mg once daily and lansoprazole 30 mg once daily groups demonstrated improvement in symptoms of reflux disease despite receiving a short course of therapy. Additionally, 69% of the lansoprazole 15 mg once daily subjects and 74% of the lansoprazole 30 mg once daily 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 30).

Table 30. Endoscopic Remission Rates (U.S. Study)

Trial	Drug	No. of Patients	% in Endoscopic Remission 0 to 3 months	% in Endoscopic Remission 0 to 6 months	% in Endoscopic Remission 0 to 12 months
1	Lansoprazole 15 mg once daily	59	83%*	81%*	79%*
	Lansoprazole 30 mg once daily	56	93%*	93%*	90%*
	Placebo	55	31%	27%	24%
2	Lansoprazole 15 mg once daily	50	74%*	72%*	67%*
	Lansoprazole 30 mg once daily	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 31).

Table 31. Endoscopic Remission Rates (European Studies)

Drug	No. of Patients	% in Endoscopic Remission 0 to 6 months	% in Endoscopic Remission 0 to 12 months
Lansoprazole 15 mg once daily	80	81.1%*	66.1%*
Lansoprazole 30 mg once daily	71	85.6%*	77.4%*
Ranitidine 300 mg twice daily	70	38.1%	29.8%

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

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 32).

Table 32. Proportion of Patients Requiring Re-Dilatation (European Study)

Time	Proportion of Patients Requiring Re-Dilatation	
	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily
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 Syndrome (ZES) 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 1 to 3 years (Table 33). 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 4 years in some patients). In most ZES 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 duodenal ulcers and/or gastric ulcers and erosive reflux esophagitis.

Table 33. Summary of the Major Results from the Principal Zollinger-Ellison Syndrome (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	49	50	56
Range	27-68	22-88	35-76
Gender (No. of Patients)			
Male	10	20	5
Female	11	10	1
Baseline BAO (mEq/h)			
Mean	38.7	32.6*	31.8
Range	9.9-143.9	5.5-96.5	13.4-64.5
Duration of Follow-up (yr)			
Mean	2.6	1.4	1.2
Range	0.5-3.8	0.2-2.5	0.1-1.6
No. of Patients with Follow-Up > than:			
> 1 year	17	17	4
> 2 years	15	11	0
> 3 years	9	0	0
No. of Patients with a Final Maintenance Visit+	20	25	5
Lansoprazole Dose/24h at Final Maintenance Visit			
Median	60	60	15
Range	30-120	30-180	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	15	20	20
Decrease	45	40	60
No Change	40	40	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		9.2	21.2
Range		5.5-17.0	8.2-36.5

\+ Final maintenance visit is defined as the last available visit incorporated into the interim data summary.

DETAILED PHARMACOLOGY

Animal

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. Chronically, famotidine is significantly less potent than lansoprazole in healing gastric ulcers and duodenal ulcers.

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 2 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 6 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 34. (For pharmacokinetic parameters of lansoprazole in humans, see ACTION AND CLINICAL PHARMACOLOGY.) Following oral or intravenous administration of a 2 mg/kg dose of racemic lansoprazole to rats and dogs, C_{max} and/or AUC values were about 2- to 3-fold 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 1 to 3 hours in mice, and 8 to 11 hours in rats and dogs.

Table 34. 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/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•h/mL)	260 - 17370	1130 - 38100	4410 - 62700

Parameter	Mouse	Rat	Dog
Oral Doses (mg/kg)	**(1.5 - 50)**	**(2-150)**	**(0.5-50)**
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
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 2 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 7 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 2- to 5-fold greater than those in plasma up to 6 hours after a 2 mg/kg intravenous 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 5 days resulted in a moderate induction of microsomal, mixed function oxidase enzymes in the liver. Microsomal protein, total cytochrome P450, and cytochrome b_5 levels were increased 12 to 45%, while activities of p-nitroanisole O-demethylase and p-nitrophenyl glucuronyltransferase were elevated about 2- to 3-fold. 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 10 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.

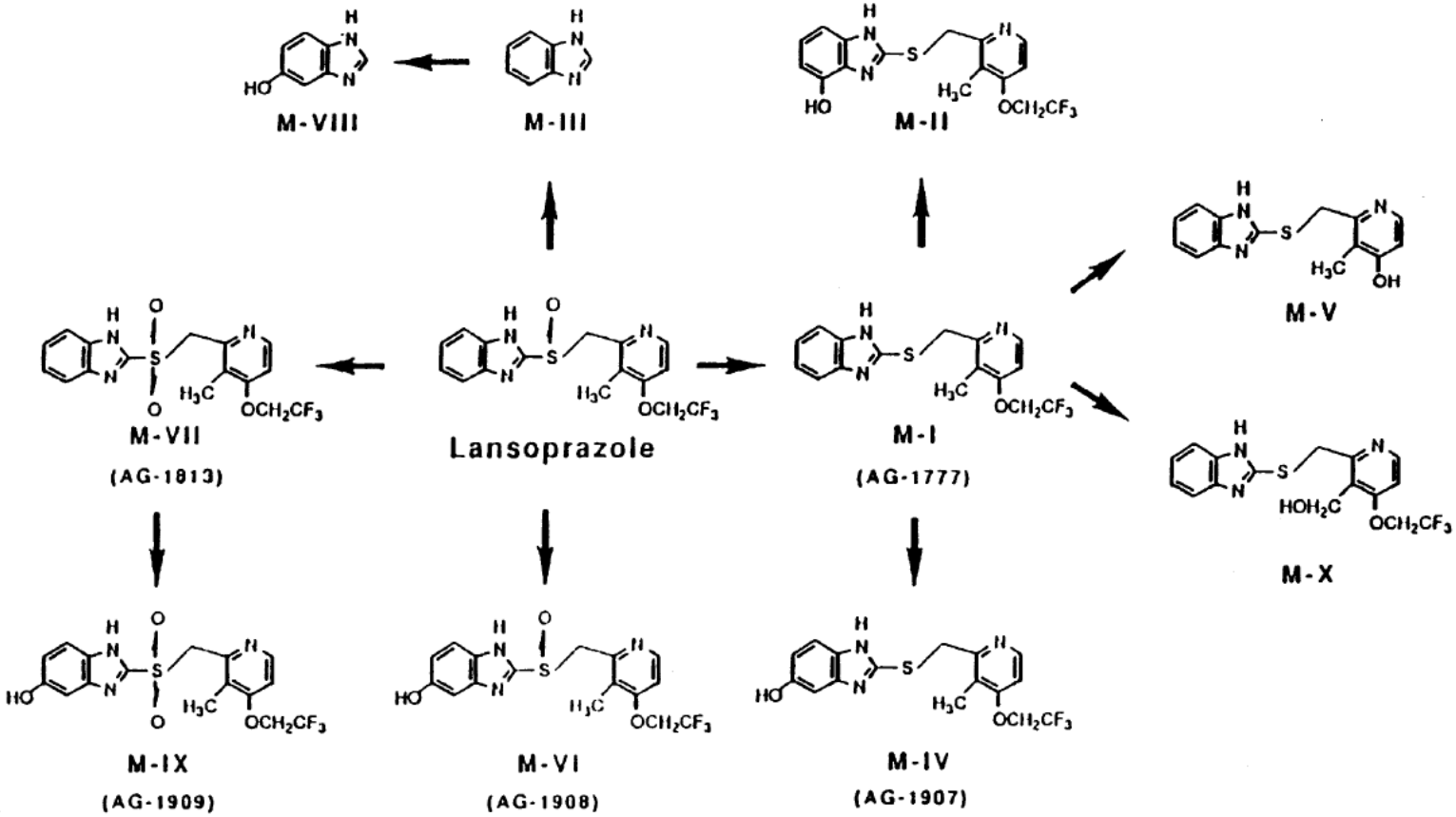


Figure 3: Postulated Metabolic Pathways of Lansoprazole in Rats and Dogs

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 excretions 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 8 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 35.

Table 35. 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;
Definitions: D = daily dosing; PO = orally dosed; IV = intravenously dosed; ID = intraduodenally dosed

Human

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 36).

Table 36. 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 to 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 post-dosing with lansoprazole 30 mg and within 1 to 2 hours postdosing with lansoprazole 15 mg and omeprazole 20 mg.

Higher levels of acid suppression have been predicted to potentiate the activity of antibiotics in eradicating *H. pylori*. The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of lansoprazole delayed-release capsules given once daily, twice daily and three times daily (Table 37).

Table 37. Mean Antisecretory Effects After 5 Days of Twice Daily and Three Times Daily Dosing of Lansoprazole

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

+ ($p < 0.05$) versus lansoprazole 30 mg once daily
* ($p < 0.05$) versus lansoprazole 30 mg once daily, 15 mg twice daily and 30 mg twice daily

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over 2 to 4 days after multiple doses. There was 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. In patients with gastric ulcer, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice; however no significant increase in nitrosamine concentrations were observed.

Enterochromaffin-like (ECL) 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 8 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 2 to 4 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 2-fold. Gastrin values returned to pretreatment levels within 4 weeks after discontinuation of therapy.

Endocrine Effects

Human studies for up to 1 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 1 year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for 2 to 8 weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily 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 2 to 8 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

Acute Toxicity

Mouse and Rat

In an acute toxicity study, lansoprazole administered via the oral, subcutaneous and intraperitoneal 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 3 routes. The LD_{50} by the oral 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 subcutaneous 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 intraperitoneal route, there were no deaths in mice at 5000 mg, but several rats of both sexes died within 2 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, subcutaneous or intraperitoneal routes.

In an acute toxicity study of several metabolites, a contaminant, and partially degraded lansoprazole (40°C and 75% relative humidity for 6 months) were determined in ICR mice. The compounds and the routes tested were pyridyl-oxide derivative (oral), sulfonyl derivative or metabolite VII (oral and intraperitoneal), thio derivative or metabolite I (oral and intraperitoneal), 5-hydroxy derivative or metabolite VI (intraperitoneal), and partially degraded lansoprazole (oral). 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 intraperitoneal 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.

Dog

In a single-dose study, 2 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.

Long-Term Toxicity

Mouse

In a 3-month study, lansoprazole was given by oral gavage to groups of 10 male and 10 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 3 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 maximum therapeutic dose was judged to be in the range of 300 to 600 mg/kg/day.

Rat

In a 3-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 7 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 4-week study, lansoprazole was administered orally by gavage to 10 Wistar rats/sex/group at dosages of 0, 15, 50, and 150 mg/kg/day (7 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 (10/sex/group) at dosages of 0, 5, 15, and 50 mg/kg/day, 7 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 2 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 4, 13, or 26 weeks. A control group was given vehicle (5% gum arabic, pH 7). There were 10 rats for each of the necropsy intervals (13 weeks treatment, 4 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 4 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 4 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 6-month study, lansoprazole was given to Sprague-Dawley rats (12/sex/group) at dosages of 0, 2, 10, and 50 mg/kg/day, 7 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 3 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 1-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, 7 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.

Dog

In a 6-month study, lansoprazole was given to 4 beagle dogs/sex/group in hard gelatin capsules at dosages of 0, 2, 10, and 50 mg/kg/day 7 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 3 months but not at 6 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 3 and 6 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, 7 days per week. There were 4 dogs/sex/group. There were 2 deaths, 1 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 electrocardiogram (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 3 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 2 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 2 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 Rat and Dog Studies

Two studies were conducted to evaluate the toxicity and toxicokinetics of lansoprazole in preadolescent rats and dogs. Selected dosages for the 2 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 2 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 2 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.

Mutagenicity and Carcinogenicity

Mutagenicity

Lansoprazole was positive in the Ames assay for bacterial mutagenicity and in the chromosomal aberration studies in human lymphocytes, but it was negative in 3 *in vivo* studies for genotoxicity. Lansoprazole was not genotoxic in the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test. 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.

Carcinogenicity

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 1 year toxicity study. Testicular Leydig cell hyperplasia and tumors were also observed. The Leydig cell changes were shown through mechanistic studies to be rat-specific and not biologically relevant to humans.

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 (1 female mouse in the 15 mg/kg/day group, 1 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).

No carcinogenic effect occurred in P53 knockout mice, which are known to be susceptible to carcinogenesis by genotoxic agents.

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 2 months of therapy. By 1 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 2-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 5 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 2 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.

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 2 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 2 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.

Reproductive studies in pregnant rats and rabbits revealed no lansoprazole-related impairment of fertility, fetal malformations or developmental toxicity to fetuses or suckling neonates. Lansoprazole is not considered to be teratogenic.

A pre- and postnatal developmental toxicity study was conducted to assess bone development, in which lansoprazole was orally administered to female rats at doses up to 100 mg/kg/day from gestation day (GD) 6 through GD 20 after birth. A reduction in body weight gain and decreased food consumption were reported during gestation and/or lactation periods at the highest dose. At necropsy on postnatal day (PND) 21, low absolute femur weight and decreases in femur and crown-rump lengths, and a decrease in growth plate thickness in the femur were reported although no histopathological findings indicating abnormal bone development were observed. These changes were considered to be secondary to overall growth suppression and not direct effects on bone development.

Juvenile Animal Toxicity Data

In a juvenile rat study, adverse effects on bone growth and development, heart valves, and male reproductive tissue were observed at lansoprazole doses higher than the maximum recommended equivalent human dose.

An eight-week oral toxicity study with a four-week recovery phase was conducted in juvenile rats with lansoprazole administered from postnatal Day 7 (age equivalent to neonatal humans) through 62 (age equivalent to approximately 14 years in humans) at doses of 40 to 500 mg/kg/day (about 1.2 to 12 times the daily pediatric dose of 15 mg in children age one to 11 years weighing 30 kg or less, based on AUC).

Changes in male reproductive tissue (testes and epididymis) occurred at a dose of 250 mg/kg/day (approximately 6 times the daily dose of 15 mg in pediatric patients based on AUC, age one to

11 years weighing 30 kg or less). Heart valve thickening occurred at a lansoprazole dose of 500 mg/kg/day (approximately 12 times the daily dose of 15 mg in pediatric patients based on AUC, age one to 11 years weighing 30 kg or less). Heart valve thickening was not observed at the next lower dose (250 mg/kg/day) and below. The findings trended towards reversibility after a four-week drug-free recovery period.

No effects on heart valves were observed in a 13-week intravenous toxicity study of lansoprazole in adolescent rats (approximately 12 years human age equivalence) at systemic exposures similar to those achieved in the eight-week oral toxicity study in juvenile (neonatal) rats.

In the eight-week oral toxicity study of lansoprazole, doses equal to or greater than 100 mg/kg/day produced delayed growth, with impairment of weight gain observed as early as postnatal Day 10 (age equivalent to neonatal humans). At the end of treatment, the signs of impaired growth at 100 mg/kg/day and higher included reductions in body weight (14% to 44% compared to controls), absolute weight of multiple organs, femur weight, femur length and crown-rump length. Femoral growth plate thickness was reduced only in males and only at the 500 mg/kg/day dose. The effects related to delayed growth persisted through the end of the 4-week recovery period. Longer term data were not collected.

In a follow-up developmental sensitivity toxicity study, juvenile rats (12 rats per treatment group) were orally administered 250 and/or 500 mg/kg/day lansoprazole for four or eight weeks starting on postnatal Day (PND) 7 (age equivalent to neonatal humans), PND 14 (age equivalent to approximately one year in humans), or PND 21 (age equivalent to approximately two years in humans).

Signs of toxicity (lower mean body weight gain and/or heart valve thickening) were observed in all dose groups of juvenile rats. Incidences of heart valve thickening were 2/12, 5/12 and 0/12, respectively, in juvenile rats in those groups dosed starting at ages 7, 14, and 21 day with 500 mg/kg/day lansoprazole for 4 weeks. Heart valve thickening in animals in those groups dosed with 500 mg/kg/day lansoprazole for eight weeks starting at PND 7, 14, and 21 were 2/12, 7/12, and 1/12, respectively.

Due to the high incidence of mortality (9 of 24 males were found dead and 15 of 24 males were euthanized between PND 18 and PND 21) in the 500 mg/kg/day dose group starting at PND 14, the 500 mg/kg/day dose groups were terminated and replaced with 250 mg/kg/day dose groups. Incidences of heart valve thickening in juvenile rats dosed with 250 mg/kg/day (approximately four times the expected lansoprazole exposure based on AUC in pediatric patients 1 to 11 years of age) starting at PND 14 were two (2/12) and one (1/12) in the four week and eight week dose groups, respectively. Incidences of the heart valve thickening were observed in almost all dose groups. Juvenile rats younger than PND 21 (age equivalent to approximately two years in humans) were more sensitive to the development of heart valve thickening.

The relevance of these findings to pediatric patients less than 12 years of age is unknown. The findings in this study are not relevant for patients 12 years of age and above.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr RIVA-LANSOPRAZOLE

Lansoprazole Delayed-Release Capsules, USP

Read this carefully before you start taking RIVA-LANSOPRAZOLE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about RIVA-LANSOPRAZOLE.

Serious Warnings and Precautions

If you are taking RIVA-LANSOPRAZOLE and clarithromycin, and you are pregnant or nursing: do not use clarithromycin unless your doctor tells you. This may harm your fetus or infant.

What is RIVA-LANSOPRAZOLE used for?

RIVA-LANSOPRAZOLE is used to treat conditions where reducing stomach acid production is needed, such as:

- **Duodenal ulcer**
  A duodenal ulcer is a sore on the lining of the duodenum, which is the beginning of the small intestine.
- **Gastric ulcer**
  A gastric ulcer is a sore on the lining of the stomach.
- **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.
- **Healing of non-steroidal anti-inflammatory drugs (NSAID)-Associated Gastric Ulcer**
- **Reduction of risk of NSAID-Associated Gastric Ulcer**
- **Symptomatic gastroesophageal reflux disease (GERD)**
  GERD 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.
- **Treatment of the bacterial infection caused by *Helicobacter pylori* (*H. pylori*) in combination with other medications (e.g., the antibiotics clarithromycin and amoxicillin) to treat stomach ulcers.**

RIVA-LANSOPRAZOLE is also indicated for the treatment of erosive and non-erosive GERD in children, aged 6 to 17 years.

How does RIVA-LANSOPRAZOLE work?

RIVA-LANSOPRAZOLE is a proton pump inhibitor (PPI).It helps reduce acid production in the stomach.

What are the ingredients in RIVA-LANSOPRAZOLE?

Medicinal ingredients: lansoprazole

Non-medicinal ingredients: D&C yellow No. 10, FD&C blue No. 1 (30 mg capsules only), FD&C green No. 3 (15 mg capsules only), FD&C red No. 3, gelatin, hydroxypropyl cellulose, hypromellose, macrogol, maize starch, magnesium carbonate, methacrylic acid-ethyl acrylate copolymer, polysorbate 80, silica colloidal anhydrous, sucrose, sugar spheres, talc, titanium dioxide.

RIVA-LANSOPRAZOLE comes in the following dosage forms:

- capsules: 15 mg and 30 mg.

Do not use RIVA-LANSOPRAZOLE if:

- you have an allergy to:
  - lansoprazole or
  - any of the nonmedicinal ingredients in RIVA-LANSOPRAZOLE (see What are the ingredients in RIVA-LANSOPRAZOLE?).
- you are taking rilpivirine

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RIVA-LANSOPRAZOLE. Talk about any health conditions or problems you may have, including:

- about all **health problems** you have now or have had in the past;
- if you have or develop **severe diarrhea**. This may be a sign of a more serious condition;
- if you have **kidney problems**;
- if you have a **stomach cancer**;
- if you have **liver problems**;
- if you experience any symptoms including palpitations (rapid heartbeat), dizziness, seizures, twitching, spasms, cramps and convulsions. These may be signs of low magnesium levels in the body;
- if you are taking **astemizole†, terfenadine†, cisapride†** (†not currently marketed in Canada)**, or pimozide**;
- if you are taking other medications (see The following may interact with RIVA-LANSOPRAZOLE);
- if you are **pregnant, trying to get pregnant, breast-feeding or planning to breast-feed**;

- If you are due to have a specific blood test (Chromogranin A).

Other warnings you should know about:

RIVA-LANSOPRAZOLE may help your acid-related symptoms. However you could still have serious stomach problems. Talk to your doctor if your problems continue.

Take RIVA-LANSOPRAZOLE exactly as your doctor tells you. You will use the lowest dose and shortest time suitable for your condition. Talk to your doctor if you have any concerns about your treatment.

Depending on your condition, your doctor may tell you to use RIVA-LANSOPRAZOLE for a longer period.

Using proton pump inhibitors like RIVA-LANSOPRAZOLE for a long time (every day for a year or longer) may increase risks of broken bones of the hip, wrist or spine. Talk to your doctor about this risk.

Long term use of proton pump inhibitors may also interfere with the absorption of Vitamin B12 from the diet. This may cause a shortage of Vitamin B12 in your body. Talk to your doctor.

Using RIVA-LANSOPRAZOLE for a long period of time may cause a growth in your stomach (polyp), especially after one year.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RIVA-LANSOPRAZOLE:

- ampicillin esters
- atazanavir
- nelfinavir
- saquinavir/ ritonavir
- clopidogrel
- digoxin
- iron salts
- ketoconazole
- methotrexate
- sucralfate
- tacrolimus
- theophylline
- warfarin

How to take RIVA-LANSOPRAZOLE:

- Take RIVA-LANSOPRAZOLE daily:
  - Before breakfast
- If your doctor tells you to take RIVA-LANSOPRAZOLE twice daily, take:
  - One before breakfast
  - One with another meal
- Do not crush or chew capsules.
- Swallow whole with water.

Usual dose:

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

Condition	Adult Dose	Child Dose	How Often	How Long
Duodenal Ulcer	15 mg	--	Once daily before breakfast	2 to 4 weeks, as directed by doctor
Triple Therapy	30 mg RIVA-LANSOPRAZOLE 500 mg clarithromycin 1000 mg amoxicillin	--	Twice daily before breakfast and another meal	7, 10 or 14 days, as directed by doctor
Gastric Ulcer	15 mg	--	Once daily before breakfast	4 to 8 weeks, as directed by doctor
Healing of NSAID-Associated Gastric Ulcer	15 to 30 mg	--	Once daily before breakfast	Up to 8 weeks, as directed by doctor
Reduction of Risk of NSAID-Associated Gastric Ulcer	15 mg	--	Once daily before breakfast	Up to 12 weeks, as directed by doctor
Reflux Esophagitis or Poorly Responsive Reflux Esophagitis Including Patients with Barrett's Esophagus	30 mg	--	Once daily before breakfast	4 to 8 weeks, as directed by doctor
Maintenance Treatment of Healed Reflux Esophagitis	15 mg	--	Once daily before breakfast	As directed by doctor

Condition	Adult Dose	Child Dose	How Often	How Long
Treatment and Maintenance of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	Starting dose: 60 mg once a day. Dose may be increased by doctor	--	Once daily before breakfast If dose is more than 120 mg per day: take in divided doses.	As directed by doctor
Gastroesophageal Reflux Disease (GERD)	15 mg	--	Once daily before breakfast	Up to 8 weeks, as directed by doctor. If symptoms do not stop within 4 to 8 weeks, talk to your doctor.
Pediatric GERD (erosive and non-erosive esophagitis)		**6 to 11 years of age** weighing: • 30 kg or less: 15 mg • over 30 kg: 30 mg **12 to 17 years of age:** take adult dose	Once daily before breakfast	Up to 12 weeks, as directed by doctor.

Overdose:

If you think you have taken too much RIVA-LANSOPRAZOLE, 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 remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time. If you are not sure about dosing, call your doctor. If you take too much RIVA-LANSOPRAZOLE, call your doctor right away.

What are possible side effects from using RIVA-LANSOPRAZOLE?

Like all medicines, RIVA-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.

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).

Tell your doctor right away if you have any of these symptoms:

- New or worsening joint pain
- Rash on your cheeks or arms that gets worse in the sun

Serious side effects from lansoprazole are uncommon.

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

Treatment in combination with antibiotics

If you experience symptoms such as severe (bloody or repeated watery) diarrhea, with or without fever, abdominal pain or tenderness, you may have bowel inflammation caused by bacterial infection (*Clostridium difficile*). If this happens, stop taking the drug combination and call your healthcare professional immediately.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON* Abdominal pain		✓	
Severe diarrhea accompanied with blood and/or mucous			✓

*Uncommon: occurring between 0.2% and 1% in clinical trials

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep RIVA-LANSOPRAZOLE out of reach and sight of children.

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

If you want more information about RIVA-LANSOPRAZOLE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website (www.labriva.com), or by calling the manufacturer, Laboratoire Riva Inc., at 1-800-363-7988.

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