Approved Date: March 9th,2012

Package Insert of Lansoprazole Enteric-coated Capsule

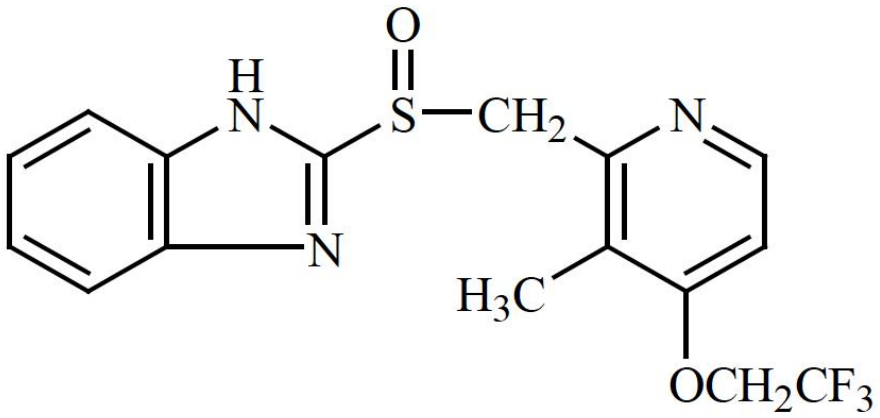
Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]

Generic Name: Lansoprazole Enteric-coated Capsules
Chinese Pinyin: Lansuolazuo Changrongjiaonang

[Active Ingredients]

The active pharmaceutical ingredient (API) of this product is Lansoprazole.
Chemical Name of the API: 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole.
Structural Formula:



Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$
Molecular Weight: 369.37

[Inactive Ingredient]

Sucrose, Corn Starch, Sucrose pellet, Magnesium Oxide, MethylMethacrylate Resin, Polyethylene glycol, Polysorbate 80, Hydroxypropylmethylcellulose, Talc Powder, Titanium Dioxide, Purified Water.

[Properties]

This product contains white or off-white enteric-coated pellets.

[Indications]

Short-Term Treatment of Active Duodenal Ulcer

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

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

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

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

Dual Therapy: LANSOPRAZOLE/amoxicillin LANSOPRAZOLE in combination with amoxicillin as dual therapy is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or

one-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected** (see the clarithromycin package insert, MICROBIOLOGY section). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Please refer to the full prescribing information for amoxicillin.

Maintenance of Healed Duodenal Ulcers

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

Short-Term Treatment of Active Benign Gastric Ulcer

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

Healing of NSAID-Associated Gastric Ulcer

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

Risk Reduction of NSAID-Associated Gastric Ulcer

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

Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

LANSOPRAZOLE is indicated for the treatment of heartburn and other symptoms associated with GERD.

Short-Term Treatment of Erosive Esophagitis

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

Maintenance of Healing of Erosive Esophagitis (EE)

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

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (ZES)

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

[Strength]
30 mg

[Dosage and Administration]

Recommended dose

Indication	**Recommended Dose**	**Frequency**
Duodenal Ulcers		
Short-Term Treatment	15 mg	Once daily for 4 weeks

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

Patients should be instructed that if a dose is 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.

Special Population

Renal impairment patients and geriatric patients do not require dosage adjustment. However, consider dose adjustment in patients with severe liver impairment.

[Adverse Reactions]

Clinical

Worldwide, over 10,000 patients have been treated with LANSOPRAZOLE enteric-coated capsules in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. In general, LANSOPRAZOLE enteric-coated capsules treatment has been well-tolerated in both short-term and long-term trials.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
The following adverse reactions were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of LANSOPRAZOLE enteric-coated capsules-treated patients and occurred at a greater rate in LANSOPRAZOLE enteric-coated capsules-treated patients than placebo-treated patients in the Table below.

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

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

[Contraindications]
KELANMEI is contraindicated in patients with known severe hypersensitivity to any component of the formulation of KELANMEI.
For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with KELANMEI, refer to the CONTRAINDICATIONS section of their package inserts.

[Precautions]
Gastric Malignancy
Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.
Clostridium difficile Associated Diarrhea
Published observational studies suggest that proton pump inhibitor (PPI) therapy like LANSOPRAZOLE enteric-coated capsules may be associated with an increased risk of Clostridium difficile associated diarrhea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.
Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
CDAD has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with KELANMEI, refer to WARNINGS and PRECAUTIONS sections of those package inserts.
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 conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.
Hypomagnesemia
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and

seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.
Concomitant Use of KELANMEI with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

[Use in Pregnant and Lactation]
Pregnancy
Teratogenic effects
Pregnancy Category B. Reproduction studies have been performed in pregnant rats at oral doses up to 40 times the recommended human dose and in pregnant rabbits at oral doses up to 16 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of lansoprazole to the mother.

[Pediatric Use]
The safety and effectiveness of LANSOPRAZOLE enteric-coated capsules have been established in pediatric patients 1 to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis, however, LANSOPRAZOLE enteric-coated capsules was not effective in patients with symptomatic GERD 1 month to less than 1 year of age in a multicenter, double-blind, placebo controlled study.
Neonate to less than 1 year of age
The pharmacokinetics of LANSOPRAZOLE enteric-coated capsules were studied in pediatric patients with GERD aged less than 28 days and 1 to 11 months. Compared to healthy adults receiving 30 mg, neonates had higher exposure (mean weight-based normalized AUC values 2.04-and 1.88-fold higher at doses of 0.5 mg/kg/day and 1 mg/kg/day, respectively). Infants aged $\leqslant$10 weeks had clearance and exposure values that were similar to neonates. Infants aged greater than 10 weeks who received 1 mg/kg/day had mean AUC values that were similar to adults who received a 30 mg dose.

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

The primary efficacy endpoint was assessed by greater than 50% reduction from baseline in either the percent of feedings with a crying/fussing/irritability episode or the duration (minutes) of a crying/fussing/irritability episode within one hour after feeding.
There was no difference in the percentage of responders between the lansoprazole pediatric suspension group and placebo group (54% in both groups).
There were no adverse events reported in pediatric clinical studies (1 month to less than 12 months of age) that were not previously observed in adults.

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

One to 11 years of age

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

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

Twenty-one of 27 erosive esophagitis patients were healed at 8 weeks and 100% of patients were healed at 12 weeks by endoscopy

GERD Symptom Improvement and Erosive Esophagitis Healing Rates in Pediatric Patients Age 1 to 11

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)

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

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

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

Twelve to 17 years of age

In an uncontrolled, open-label, U.S. multicenter study, 87 adolescent patients (12 to 17 years of age) with symptomatic GERD were treated with LANSOPRAZOLE enteric-coated capsules for 8 to 12 weeks. Baseline upper endoscopies classified these patients into two groups: 64 (74%) nonerosive GERD and 23 (26%) erosive esophagitis (EE). The nonerosive GERD patients received LANSOPRAZOLE enteric-coated capsules 15 mg daily for 8 weeks and the EE patients received LANSOPRAZOLE enteric-coated capsules 30 mg daily for 8 to 12 weeks. At baseline, 89% of these patients had mild to moderate overall GERD symptoms (assessed by investigator interviews). During 8 weeks of LANSOPRAZOLE enteric-coated capsules treatment, adolescent patients experienced a 63% reduction in frequency and a 69% reduction in severity of GERD symptoms based on diary results.

Twenty-one of 22 (95.5%) adolescent erosive esophagitis patients were healed after 8 weeks of LANSOPRAZOLE enteric-coated capsules treatment. One patient remained unhealed after 12 weeks of treatment.

GERD Symptom Improvement and Erosive Esophagitis Healing Rates in Pediatric Patients Age 12 to 17

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

In these 87 adolescent patients, increases in serum gastrin levels were similar to those observed in adult studies, median fasting serum gastrin levels increased 42% from 45 pg/mL at baseline to 64 pg/mL [interquartile range (25th to 75th percentile) of 44 to 88 pg/mL] at the final visit. (Normal serum gastrin levels are 25 to 111 pg/mL.)
The safety of LANSOPRAZOLE enteric-coated capsules has been assessed in these 87 adolescent patients. Of the 87 adolescent patients
with GERD, 6% (5/87) took LANSOPRAZOLE enteric-coated capsules for less than 6 weeks, 93% (81/87) for 6 to 10 weeks, and 1% (1/87) for greater than 10 weeks.
The most frequently reported (at least 3%) treatment-related adverse reactions in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this package insert as occurring in less than 1% of adult patients, was reported in this study by 3 adolescent patients with nonerosive GERD, who had dizziness concurrently with other reactions (such as migraine, dyspnea, and vomiting).

[Geriatric Use]

No dosage adjustment of LANSOPRAZOLE enteric-coated capsules is necessary in geriatric patients. The incidence rates of LANSOPRAZOLE enteric-coated capsules -associated adverse reactions and laboratory test abnormalities are similar to those seen in younger patients.

[Drug Interactions]

LANSOPRAZOLE enteric-coated capsules may interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).
LANSOPRAZOLE enteric-coated capsule is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that LANSOPRAZOLE enteric-coated capsule does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.
Atazanavir: LANSOPRAZOLE enteric-coated capsules cause long-lasting inhibition of gastric acid secretion. LANSOPRAZOLE enteric-coated capsules substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, LANSOPRAZOLE enteric-coated capsules, or other proton pump inhibitors, should not be co-administered with atazanavir.
Theophylline: When LANSOPRAZOLE enteric-coated capsule was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when LANSOPRAZOLE enteric-coated capsule is started or stopped to ensure clinically effective blood levels.
Warfarin: In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including LANSOPRAZOLE enteric-coated capsule, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.
Methotrexate and 7-hydromethotrexate: In an open-label, single-arm, eight-day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly),

administration of 7 days of naproxen 500 mg twice daily and LANSOPRAZOLE enteric-coated capsule 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse reactions were noted. However, this study was conducted with low doses of methotrexate. A drug interaction study with high doses of methotrexate has not been conducted.

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

Clopidogrel: Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with LANSOPRAZOLE enteric-coated capsule 30 mg (n=40), for 9 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 14% (mean AUC ratio was 86%, with 90% CI of 80 to 92%) when LANSOPRAZOLE enteric-coated capsule was coadministered compared to administration of clopidogrel alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mcM ADP) was related to the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

[Over-Dosage]
LANSOPRAZOLE enteric-coated capsule is not removed from the circulation by hemodialysis. In one reported overdose, a patient consumed 600 mg of LANSOPRAZOLE enteric-coated capsule with no adverse reaction. Oral LANSOPRAZOLE enteric-coated capsule doses up to 5000 mg/kg in rats [approximately 1300 times the 30 mg human dose based on body surface area (BSA)] and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

[Pharmacology and Toxicology]

Clinical Pharmacology

Mechanism of Action

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

[Pharmacokinetics]
LANSOPRAZOLE enteric-coated capsules contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. After a single-dose administration of 15 mg to 60 mg of oral lansoprazole, the peak plasma concentrations (C_{max}) of lansoprazole and the area under the plasma concentration curves (AUCs) of lansoprazole were approximately proportional to the administered dose. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

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

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

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

Elimination: Following single-dose oral administration of LANSOPRAZOLE enteric-coated capsules, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of 14C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m2) basis of a 50 kg person of average height [1.46 m^2 body surface area (BSA)] given the recommended human dose of 30 mg/day. Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.
In a 24-month carcinogenicity study, CD-1 mice were treated with oral lansoprazole doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on BSA) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on BSA).
A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.
Lansoprazole was positive in the Ames test and the in vitro human lymphocyte chromosomal aberration assay. 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.
Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

Animal Toxicology and/or Pharmacology
Reproductive Toxicology Studies
Reproduction studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day [40 times the recommended human dose (30 mg/day) based on body surface area (BSA)] and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

[Storage]
Seal and store in a dry place.

[Packaging]
Aluminum-plastic blister packaging
1. 15 mg capsules:
   6 capsules/plate/carton; 7 capsules/plate/carton; 10 capsules/plate/carton; 12 capsules/2 plates/carton; 14 capsules/2 plates/carton; 20 capsules/2 plates/carton; 28 capsules/4 plates/carton.
2. 30 mg capsules:
   6 capsules/plate/carton; 7 capsules/plate/carton; 10 capsules/plate/carton; 12 capsules/2 plates/carton; 14 capsules/2 plates/carton; 20 capsules/2 plates/carton; 28 capsules/4 plates/carton.

[Shelf-Life]
24 months

[Executive Standard]
National Medical Products Agency Standard YBH00472012

[Approval Number]
1. Guo Yao Zhun Zi H20123069
2. Guo Yao Zhun Zi H20123070

[Manufacturer]
Company Name: Beijing Honglin Pharmaceutical Inc.
Production Address: Beijing Yanqui Economic Development Area, Huairou District ,Beijing 101407, P.R. China
Tel: 86-010-61669962
Fax: 86-010-61669843
Website: http://www.osihl.com