Lylian®

Ilaprazole

Product name

Generic name: Ilaprazole Enteric-coated Tablets

Description

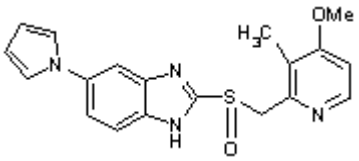
Ilaprazole is an enteric-coated tablet and is white or off-white when the coating is removed.

Composition

Each tablet contain:

Ilaprazole 5 mg

Chemical name: 5 - (1H - pyrrole - 1 - base) – 2 - [[(4 - methoxy - 3 - methyl) - 2 – pyridyl] - methyl] - sulfinyl - 1H - benzimidazole

Chemical formula: 

Molecular formula: $C_{19}H_{18}N_4O_2S$

Molecular weight: 366.43

Excipients

Eudragit L30D, Magnesium Stearate, Titanium Dioxide, Sunset Yellow Aluminum Lake etc.

Indications

It is indicated for the treatment of duodenal ulcer and reflux esophagitis.

Dosage and Administration

Ilaprazole is used for the treatment of duodenal ulcer and reflux esophagitis in adults. Swallow Ilaprazole Enteric-coated Tablets with water in every morning before meal; do not chew.

1. For the treatment of duodenal ulcer:

   10 mg once daily for consecutive 4 weeks, or use it as directed by your doctor.

2. For the treatment of reflux esophagitis:

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10 mg once daily for consecutive 4 weeks. If not healed, patients are recommended to take an additional 4-week treatment; if healed but still have persistent symptoms, patients are recommended to adjust the dosage to 5 mg daily for additional 4-week, or take the drug as directed by the doctor.

Contraindications

It is contraindicated in patients with known hypersensitivity to any component of the formulation.

It is contraindicated in patients with known hypersensitivity to Ilaprazole and other benzimidazoles.

Precautions

1. Swallow Ilaprazole Enteric-coated tablet whole. Do not chew or crush the tablets.
2. It is not recommended to treat general peptic ulcer by large dosage and/or long-term usage of Ilaprazole due to its strong inhibiting effect on gastric acid secretion.
3. Malignant lesions of stomach and esophagus should be excluded before using the product, so as not to delay the diagnosis due to symptomatic relief.
4. Use with caution in patients with renal and hepatic impairment, as clinical data are insufficient for this group of patients.
5. Patients expected to be on prolonged treatment of PPI should pay attention to the possibility of fracture risk, especially in the elderly, and a regular monitoring on magnesium levels should be considered to prevent the occurrence of hypomagnesaemia.
6. Patients taking Clopidogrel should pay attention to the interaction with proton pump inhibitors and the safety issue should be discussed with your doctor in advance to make sure that the concomitant use is safe.
7. Clostridium difficile associated diarrhea

   Published observational studies suggest that PPI therapy may increase the risk of C. difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered if diarrhea does not improve.

Drug Interactions

1. Since Ilaprazole inhibits gastric acid secretion, which will affect the bioavailability of medicinal drugs whose absorption depends on the gastric pH, such as ketoconazole, itraconazole etc., its dosage should be adjusted in the case of concomitant medication or the concomitant medication should be avoided.

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2. The results of in vitro and metabolic studies indicate that CYP3A4 enzyme is involved in the metabolism of Ilaprazole. However, currently it is uncertain whether CYP3A4 enzyme is the main metabolic enzyme of this product. It is shown from foreign studies that after oral administration of Ilaprazole 40 mg once daily for 5 days in 24 healthy subjects, the plasma concentration of midazolam, the specific substrate of CYP3A4 enzyme, is increased by 31 – 41%, indicating that Ilaprazole belongs to poor inhibitor of CYP3A4 enzyme, so it is further speculated that Ilaprazole has little effect on the metabolism of the drugs which are metabolized by CYP2C19 enzyme (such as diazepam, citalopram, imipramine, phenytoin sodium, clomipramine, etc.). At present, there is no definite data to indicate whether this product is metabolized by liver CYP2C19 enzyme, however, it is suggested from existing clinical data that the polymorphism of CYP2C19 enzyme in human body does not affect the efficacy of this product.
3. Compared the pharmacokinetic parameters obtained from concomitant use of Ilaprazole (5 mg/time, twice daily) with clarithromycin (500 mg/ time, twice daily) and amoxicillin (1 g/time, twice daily) with those obtained from single use of Ilaprazole, Ilaprazole's $AUC_{0-\infty}$ decreased by approximately 8.2 % (90% CI: 70.7% ~ 100.1%), Ilaprazole's C_{max} decreased by about 29.4% (90% CI: 58.3% ~ 80.5%); and Clarithromycin's $AUC_{0-\infty}$ did not change (90% CI: 80.1% ~ 120.9%), Clarithromycin's C_{max} increased by about 24.4% (90% CI: 100.7% ~ 149.2%).

Pregnancy and Nursing Women

Currently, there are no adequate clinical studies with Ilaprazole in pregnant and nursing woman, so they are not recommended to use this product. If it's necessary to use Ilaprazole in nursing women, breast-feeding should be suspended during the treatment.

Pediatric Use

Prohibition of use in young children and infant since no clinical data are available.

Geriatric Use

Ilaprazole should be used with caution in elderly patients whose capacity of gastric acid secretion and other physiological functions of elderly patient may be reduced generally. The clinical trial results indicate that there is no significant difference in safety and efficacy between elderly patients and general population.

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Adverse Reactions

The following adverse reactions are reported in clinical trials of duodenal ulcer and reflux esophagitis. The adverse reactions were usually mild or moderate and can be recovered spontaneously. The longest treatment course of phase III clinical trial which has been completed is 8 weeks, and safety data for using longer than 8 weeks are not available at present.

Duodenal ulcer (Phase II and III: A total of 507 subjects involved)	
Common adverse reactions (>1/100, <1/10)	Diarrhea (2.4%), headache and dizziness (2.4%), hepatic function abnormal (ALT and AST elevation) (1.8%)
Rare adverse reactions (>1/1,000, <1/100)	Rash, urticaria, low back pain, abdominal distension, dry mouth and bitter taste, heart palpitations, chest tightness, prolonged menstruation, abnormal urine routine (proteinuria), increased urea nitrogen level, abnormal electrocardiogram (ventricular premature contraction, first degree auriculo-ventricular block), abnormal blood routine (leukopenia) etc.
Reflux esophagitis: (Phase II and III: A total of 535 subjects involved)	
Common adverse reactions (>1/100, <1/10)	hepatic function abnormal (ALT and AST elevation) (6.7%), gastrointestinal discomfort (2.6%), dizziness (2.1%), and rash (1.1%).
Rare adverse reactions (>1/1,000, <1/100)	Diarrhea, nausea/vomiting, dry mouth, abdominal distension, constipation, fatigue, lethargy, chest tightness, muscle and joint discomfort, abnormal blood routine (decreased WBC) and urine routine (proteinuria), and allergic rhinitis.

Overdose

Currently, there is no experience in overdose of Ilaprazole. No abnormality was observed when healthy volunteers were given single dose of 40 mg Ilaprazole in the clinical study. If over-exposure occurs accidentally, symptomatic and supportive treatment should be carried out immediately.

Pharmacology and toxicology

Pharmacological mechanism

Ilaprazole is an irreversible proton pump inhibitor, which belongs to the benzimidazole. After oral administration, Ilaprazole selectively enters the gastric parietal cells and is converted to the active metabolite sulfenamide which will react with the sulphydryl on the H^+/K^+-ATPase to form the disulfide bond and inhibits the H+/K+-ATPase to further play the role of gastric acid inhibition.

Genotoxicity

The results of CHL cell chromosome aberration test and Ames test on Ilaprazole are positive. The result of micronucleus test in mice is negative.

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Reproductive toxicity

The rats were orally given 20, 80, 160, 320 mg/kg of this product from day 6 to day 17 of pregnancy, and no other abnormality was observed except that there is a slight increase in animal preimplantation loss.

Male rats were orally given this product for 63 days before mating, during mating and 2 weeks after the end of mating period. The female rats were orally given the product for 14 days before mating, during mating until day 17 of pregnancy. When the dosage is up to 320 mg/kg, the abnormal rate of shape and viscera in fetal rat increased, including small eyes, sub-arachnoid gap enlargement, gastroschisis, genital malformation, short body, edema, no gap's anus, abnormal upper and lower limbs, defective ossification of occipital bone, defective ossification of one or more thoracic ossification centers, ossification failures of the fifth metacarpal bone.

The rats were given the product by oral administration from day 6 of pregnancy to day 21 after delivery, and the F1 generation rats (1,000 mg/kg group) were observed with rough body hair, depilation, and ossification delay. The liver weight of F1 generation rat (200 mg/kg and 1,000 mg/kg group) was significantly reduced. F1 generation female rats were examined after pregnancy, and it was found that the number of corpus luteum, implantation and alive fetuses were all decreased.

Carcinogenicity:

P53 (+ /-) mice were given this product by oral administration for consecutive 26 weeks, the weight of the stomach was increased at the doses of 16 and 64 mg/kg/d, and basal mucosal hyperplasia was observed by pathological examination. F344 rats were given this product by oral administration for consecutive 24 months, benign and malignant neuroendocrine tumors were found in gastric gland of rats at the doses of 43 and 138 mg/kg/d. This result is similar to other proton pump inhibitors.

Pharmacokinetics

The pharmacokinetics results showed that 5 mg, 10 mg, 20 mg single oral dose of the product was given to the subjects in the morning before meals, as a result, C_{max} and AUC increased with the dose increasing, and the process of Ilaprazole in the human body basically complied with linear dynamic characteristics. No prototype drug was detected in the urine of subjects.

The subjects were orally given the products for consecutive 7 days with 10 mg daily. It is indicated that pharmacokinetic parameters of Ilaprazole after multiple dose administration have no significant change compared to single dose administration, and there is no accumulation in vivo. After oral administration for consecutive more than 4 days, the concentration of Ilaprazole in plasma will reach a steady state. Compared with fasting, feeding will delay the T_{max} of plasma

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concentration of Ilaprazole, but it has little effect on other pharmacokinetic parameters.

Clinical trials

1. Suppressing effect on gastric acid secretion

12 healthy volunteers were involved in this study. The suppressing effect on gastric acid secretion is in a dose dependent manner, the details are shown in Table 1.

Table 1. 24-hour intragastric pH-time profile on day 1 in healthy subjects

	Time percentage of pH ≥ 4	Time percentage of pH ≥ 4 (night)	Population percentage that pH ≥ 4 maintained at least 16 hours
Ilaprazole 5mg	80.36 %	79.10 %	25.00 %
Ilaprazole 10 mg	88.11 %	95.16 %	41.67 %
Ilaprazole 20 mg	91.02 %	94.46 %	75.00 %
Omeprazole 20 mg	76.61 %	68.06 %	8.33 %

The results of 24-hour intragastric pH monitoring in subjects with duodenal ulcer show that time percentage of pH ≥ 3 on day 5 is 93.8% in 5 mg Ilaprazole group, meeting the requirements of acid suppression in the treatment of peptic ulcer. Results are shown in Table 2.

Table 2. 24-hour intragastric pH-time profile on day 5 in duodenal ulcer patient (median)

	Time percentage of pH ≥ 3	Time percentage of pH ≥ 4	Time percentage of pH ≥ 5	24 hours pH	pH at night
Ilaprazole 5 mg (n=11)	93.80%	86.60%	76.20%	6.00	5.60
Ilaprazole 10 mg (n=10)	98.70%	97.75%	93.25%	6.40	6.60
Omeprazole 20 mg (n=10)	95.10%	92.65%	81.45%	6.30	5.80

2. Clinical trials

2.1 A multicenter, randomized, double-blind, double-dummy positive controlled phase III clinical trial was performed for duodenal ulcer treatment. The subjects enrolled were grouped as 10 mg Ilaprazole test group and 20 mg Omeprazole control group and were given test drugs once daily in the morning for consecutive 4 weeks. The healing of ulcer was observed at the end of week 2 and week 4 after treatment. Results are shown in Table 3.

Table 3. The healing rate of duodenal ulcer in phase III clinical trial

	Healing rate of 2 weeks' treatment	Healing rate of 4 weeks' treatment	Cure rate of 4 weeks' treatment
Ilaprazole 10 mg (n=330)	77.88%	93.03%	84.55%

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Omeprazole 20 mg (n=164)	75.00%	90.85%	82.32%

2.2 A randomized, double-blind, double-dummy multicenter, positive controlled clinical study was performed on different doses of Ilaprazole in the treatment of duodenal ulcer. The subjects enrolled were grouped as 5 mg Ilaprazole group, 10 mg Ilaprazole group and 10 mg Rabeprazole control group, and were given test drugs once daily in the morning before meal for consecutive 4 weeks. The healing rate of ulcer was observed at the end of week 2 and week 4 after administration. Results are shown in Table 4.

Table 4. The healing rate of duodenal ulcer in dose-effect relationship clinical trial

	Healing rate of 2-week- treatment	Healing rate of 4-week- treatment	Cure rate of 4- week-treatment
Ilaprazole 5 mg (n=131)	67.18%	90.08%	77.86%
Ilaprazole 10 mg (n=129)	75.97%	91.47%	83.72%
Rabeprazole 10 mg (n＝130)	68.46%	90.77%	75.38%

2.3 A multicenter, randomized, double-blind, double-dummy and positive controlled phase III clinical study was performed for reflux esophagitis treatment. The subjects enrolled were grouped as 10 mg Ilaprazole test group and 40 mg esomeprazole control group, and were given test drugs 30 minutes before breakfast with warm water, once daily for 4 consecutive weeks. For subjects who healed from 4 weeks' treatment, they were given half dose of the test drug continually for additional 4 weeks. For subjects who did not healed from 4 weeks treatment, they were given original dose of the test drug continually for additional 4 weeks. The healing of esophageal mucosa under gastroscopy was observed at week 4 and week 8. Results are shown in Table 5.

Table 5. The healing rate of reflux esophagitis in phase III clinical trial

	Healing rate of 4 weeks treatment	Healing rate of 8 weeks treatment
Ilaprazole 10 mg (n=322)	76.09%	83.54%
Esomeprazole 40 mg (n=215)	77.67%	82.79%

For LA-C and LA-D baseline subjects in phase III clinical trials, 4-week healing rates of 10 mg Ilaprazole group and 40 mg esomeprazole group were 40% (7/18) and 60% (9/15) respectively, and 8-week healing rates of 10 mg Ilaprazole group and 40 mg

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esomeprazole group were 50% (9/18) and 80% (12/15), respectively. The results should be interpreted carefully due to the small sample size.

Storage

Protect from light, keep sealed and do not store above 30°C.

Package

Oral solid pharmaceutical polypropylene bottle: 6 enteric coated tablets per bottle.

No. Reg. :

Shelf life

36 months.

Imported by

PT. Harsen Laboratories
Jl. Raya Bogor Km. 24,6 Jakarta Timur
DKI Jakarta, Indonesia 13750

Manufacturer

Manufacturer name: Livzon (Group) Pharmaceutical Factory

Manufacturer address: No.38 Chuangye Road North, Jinwan District, Zhuhai, Guangdong, P.R. China.

Postal Code: 519045

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