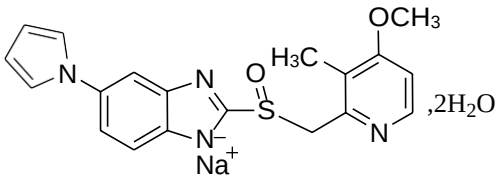
Leaflet of Ilaprazole Sodium for Injection

Please read the instructions carefully and use it under the guidance of a physician

[NAME OF THE MEDICINAL PRODUCT]
Generic Name: Ilaprazole Sodium for Injection
Brand Name: Lylian
English Name: Ilaprazole Sodium for Injection

[INGREDIENTS]
The active ingredient is Ilaprazole Sodium.
Chemical Name: 5-(1*H*-pyrrol-1-yl)-2-[[(4-methoxy-3-methyl-2-pyridyl)-methyl]sulfinyl]-1*H*-benzimidazole sodium dihydrate
Chemical Structural Formula:



Molecular Formula: $C_{19}H_{17}N_4NaO_2S \cdot 2H_2O$
Molecular Weight: 424.45

[DESCRIPTION]
The product is white or off-white loose cakes or powder.

[INDICATION]
Peptic ulcer bleeding.

[STRENGTH]
10 mg (calculated based on $C_{19}H_{18}N_4O_2S$).

[DOSAGE AND ADMINISTRATION]
The product is given intravenously at an initial dose of 20 mg, followed by 10 mg once per day for two consecutive days. Oral medication may be appropriate after the course of treatment.

Precautions in use:

1. Endoscopic hemostasis should be taken into account as a priority in populations who are at a high risk of squirt bleeding or extravasation bleeding, and who are endoscopically observed with visible vessels.

2. The product is used for intravenous infusion: reconstitute 10 mg thoroughly with 100 ml of 0.9% sodium chloride solvent, and give intravenously within 30 minutes through an infusion device. When the drug is given at an initial dose of 20 mg, the product should be thoroughly reconstituted in 200 ml of 0.9% sodium chloride solvent. The drug should be used within 3 hours after preparation.

3. This product can only be reconstituted with 0.9% sodium chloride solvent for intravenous infusion. The prepared solution cannot be used in a pharmacy admixture program.

[ADVERSE REACTIONS]

355 patients in a Phase III clinical trial were given Ilaprazole Sodium for Injection intravenously, once daily, with the initial dose of 20 mg followed by 10 mg for a course of 3 days. A total of 18 adverse drug reactions (ADRs) were observed. Common ADRs[1] included an increase in ALT and AST (2.82%), and a decrease in leukocyte (1.97%). An increase in ALP (0.28%), γ-GT (0.28%) and total bilirubin (0.28%) were rarely observed[2]. The ADRs observed were mild or moderate and patients can recover spontaneously. The 3-day treatment was the maximum course performed in the Phase III clinical trial, and no more data on safety is available.

[CONTRAINDICATIONS]

Hypersensitivity to Ilaprazole or other benzimidazole compounds, or any other ingredients in this product.

[WARNINGS AND PRECAUTIONS]

1. The product is for intravenous infusion only, and intramuscular injection is prohibited.
2. Other antacids should not be used concomitantly due to the strongly and sustained effect on gastric acid suppression.
3. Absorption profile of certain drugs may be affected because Ilaprazole Sodium for Injection can significantly increase the intragastric pH.
4. Patients with hepatic and renal dysfunction should be treated with caution because no adequate clinical data is available from the use of Ilaprazole Sodium for Injection.
5. Malignant lesions of the stomach and esophagus should be excluded before using the product, so as not to delay the diagnosis due to symptomatic relief. Patients should be closely monitored during the treatment with the product, and other therapeutic actions should betaken when the treatment is demonstrated to be ineffective.
6. Co-administration of Clopidogrel and proton pump inhibitors is not recommended, a request to your doctor is necessary when the combination of Clopidogrel and proton pump inhibitors is judged unavoidable to make sure the co-administration is safe.
7. The effectiveness and safety of Ilaprazole Sodium for Injection for more than 3 days have not been demonstrated.

[1] Occurrence rate ≧1/100 and < 1/10.
[2] Occurrence rate ≧1/1000 and < 1/100.

[PREGNANCY AND LACTATION]

Currently, no clinical data is available for pregnant and lactating women. It is not recommended for pregnant and lactating women to use this product. If there is a clear need to a nursing woman, breast-feeding should cease during the treatment.

[PEDIATRIC POPULATION]

Clinical data in children is not available.

[GERIATRIC POPULATION]

In the clinical trial of this product, 45 elderly patients over 60 years of age were treated with Ilaprazole Sodium for Injection, and the clinical trial results have indicated that the safety and efficacy of geriatric population were not significantly different from those of general population.

[DRUG INTERACTIONS]

1. Since the increased gastric pH during Ilaprazole treatment may influence the absorption profile of other drugs (e.g., Ketoconazole, Itraconazole etc.), concomitant administration isnot recommended or dosage adjustment should be considered when co-administration is unavoidable.

2. The results of in vitro study and metabolic study indicated that CYP3A4 enzyme plays a role in Ilaprazole metabolism, but it has not identified that the CYP3A4 enzyme act as the main metabolic enzyme of this product. 24 healthy volunteers results in foreign clinical study showed that plasma concentration of specific substrates midazolam of CYP3A4 enzymeincreased from 31% to 41 % when they were orally given Ilaprazole 40 mg, once daily for a successive 5 days. This indicated that Ilaprazole is a weak inhibitor of CYP3A4 enzyme and,it is speculated that, the drug may be negligibly impacted the metabolism of the drugs which are metabolized by CYP2C19 enzyme (such as Diazepam, Citalopram, Imipramine, Phenytoin Sodium, Clomipramine, etc.). At present, no confirmative data is available on whether or not the product is metabolized by CYP2C19 enzyme, but the available clinicaldata indicated that the efficacy of Ilaprazole Sodium for Injection was not influenced by the polymorphism of CYP2C19 enzyme.

3. Pharmacokinetic parameters of Ilaprazole (5 mg twice daily) in co-administration of Clarithromycin (500 mg twice daily) and Amoxicillin (1 g twice daily) were compared with those of single use, the results showed that the systemic exposure of Ilaprazole ($AUC_{0-\infty}$ and C_{max}) decreased by about 8.2% (90% CI: 70.7%-100.1%) and 29.4% (90% CI: 58.3%-80.5%); $AUC_{0-\infty}$ of Clarithromycin remained unchanged (90% CI: 80.1%-120.9%), and C_{max} of which increased by about 24.4% (90% CI: 100.7%-149.2%).

4. Co-administration of Reyataz/Viracepy and Ilaprazole Sodium is not recommended, as there were evidences that the plasma concentration of Reyataz/Viracepy significantly decreased and drug resistance was observed when they were co-administered with PPIs.

[OVERDOSE]

There is very limited experience to date with deliberate overdose. No unfavorable events were observed when healthy volunteers were single dosed with 30 mg of Ilaprazole Sodium which was the maximum dose applied in the clinical study. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

[CLINICAL PHARMACOLOGY]

1. Acid antisecretory activity

The results obtained from 24-hour intragastric pH monitoring program after dosing in 20 patients with duodenal ulcer showed that the time that intragastric pH ≥ 6 on Day 1 was 20.87 h, as compliant with the clinical therapeutic requirement for bleeding of duodenal ulcer. The results also showed that time that intragastric pH ≥ 6 on Day 3 was 22.57 h and no attenuation of effect was observed when treatment duration prolonged. The results are presented in Table 1.

Table 1. 24-hour Intragastric pH monitoring on Day 1 and Day 3 of Dosing in Patients with Duodenal Ulcer (Median)

Group (Regimen)	Time	Time (h) Gastric pH ≥ 6 within 24 h
Ilaprazole Sodium for Injection (10 patients, 10 mg once daily, initial at 20 mg)	Day 1	20.87
	Day 3	22.57
Esomeprazole Sodium for Injection (10 patients, 40 mg once, twice daily)	Day 1	20.11
	Day 3	22.14

2. Clinical trial

A multicenter, randomized, double-blind, double-dummy, active-controlled Phase III study was conducted in patients who are endoscopically diagnosed with peptic ulcer bleeding, including gastric or duodenal ulcers. Endoscopic hemostasis was taken for patients at a high risk of intragastric rebleeding, as recommended in clinical guidance and was not performed for patients at a low risk of intragastric rebleeding. For both populations, intravenous infusion

was given after diagnosis. Patients in the test group were intravenously given Ilaprazole Sodium for Injection at an initial dose of 20 mg, followed by 10 mg once per day while patients in active-controlled group were given Omeprazole in the same manner 40 mg, twice daily. The treatment course were 3 days, and oral administration of Ilaprazole Enteric-coated tablets was given to both groups after 3-day treatment. The results showed that 72-hour hemostatic rate of were 95.49% (339/355) in the test group and 95.51% (170/178) in the active-controlled group, respectively.

[PHARMACOLOGY AND TOXICOLOGY]

Pharmacological Action

Ilaprazole is an irreversible proton pump inhibitor, 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. Ilaprazole converted in the acidic compartment of the parietal cell forming the active inhibitor, the sulphenamide, which covalently bonded with H^+/K^+-ATPase enzyme thereof the acid production was blocked.

Toxicological study

Genotoxicity: Ilaprazole Ames test and CHL cell chromosome aberration test showed positive results, and mouse micronucleus test showed negative results.

Reproductive toxicity: In the examination of dams during Day 6 to Day 17 of gestations, a slight increase in the pre-implantation losses were observed when female rats were orally dosed 20 mg/kg, 80 mg/kg, 160 mg/kg and 320 mg/kg, while no other abnormalities were observed. In the examination of fetuses conducted at the same time, the external malformations were found in 320 mg/kg group, including small eye ball, subarachnoid space enlargement, gastroschisis, external genital deformity, small body size, generalized edema, gapless anus, upper and lower extremity abnormalities, incomplete ossification of occipital bone and one or more sternal centers, and ossification failure of the fifth metacarpal bone, etc., when Ilaprazole Sodium was orally given to male rats 63 days prior to mating, during the mating period, and 2 weeks after mating, and to female rats 14 days prior to mating, during the mating period and the early gestation period (until day 17 of gestation). Coarse hair and alopecia, and even delayed ossification were observed in F1 rats in the 1000 mg/kg group when Ilaprazole Sodium was orally given to female rats from Day 6 of gestation to postpartum Day 21. Liver weight was significantly reduced in the F1 rats in the 200 and 1000 mg/kg group while a decrease in the number of corpora lutea, the number of implantations and live fetuses were found in the F1 female rats at post-pregnancy examination.

Carcinogenicity: Pathologically fundic mucosal hyperplasia was observed while stomach weight increased at doses of 16 and 64 mg/kg/day when p53 (+/-) mice were administered Ilaprazole by daily oral gavage for successive 26 weeks. Non-neoplastic and malignant neuroendocrine tumors were found in the glandular stomach when F344 rats were administered Ilaprazole at doses of 43 and 138 mg/kg/day by daily oral gavage for successive 24 months. These results are similar to other proton pump inhibitors.

[PHARMACOKINETICS]

The pharmacokinetic parameters of Ilaprazole in healthy subjects following single dosed Ilaprazole Sodium for Injection 20 mg as intravenous infusion were as follows: apparent volume of distribution (Vd) 13.6 L, 97% bound to plasma protein, 3.3 hours of plasma elimination half-life, 3.0 L/h of plasma clearance (CL). Ilaprazole Sodium present linear pharmacokinetics in vivo when it was given at a dose range of 5 -20 mg.

No accumulation was observed when Ilaprazole Sodium were given as intravenous infusion at a dose of 10 mg once daily for a successive 5 days.

Less than 1% (0.006%-0.008%) of parent drug was excreted in the urine when Ilaprazole Sodium was single dosed. It indicated that parent drug does not eliminate via urine.

Plasma clearance (CL) was approximately 4.1 L/h in patients with duodenal ulcer when Ilaprazole Sodium was intravenously given at a dose of 20 mg, and in those patients the systemic exposure was slightly lower, comparing against that of healthy subjects.

[COMPOSITION]

Ilaprazole Sodium
Mannitol
Disodium Edetate
Sodium Hydroxide

[STORAGE]

Keep sealed, protect from light and store at temperature not exceeding 25^{o}C.

[PACKAGING]

Primary packaging components: neutral borosilicate glass tubing and polytetrafluoroethylene/ ethylene copolymer filmed chlorobutyl rubber stopper and aluminum-plastic combination cap.
1 vial/box.
Reg. No.:

[SHELF LIFE]

24 months.

[IMPORTED BY]

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

[MANUFACTURER]

Livzon (Group) Pharmaceutical Factory
Address: No. 38 Chuangye North Road, Jinwan District, Zhuhai, Guangdong, P.R. China
Postcode: 519045
Tel: 8008301238 (free)/0756-8135620
Fax: 0756-8870128
Website: www.livzon.com.cn

INFORMASI PRODUK UNTUK PASIEN

Lylian®, 10 mg, Serbuk Injeksi Liofilisasi

Ilaprazole Sodium

Informasi umum tentang penggunaan Lylian® yang aman dan efektif.
JANGAN menggunakan Lylian® untuk kondisi yang tidak diresepkan. JANGAN memberikan Lylian®kepada orang lain, meskipun mereka memiliki gejala yang sama dengan Anda, itu dapat merugikan mereka.
Informasi produk untuk pasien ini merangkum informasi terpenting tentang Lylian®. Jika Anda membutuhkan informasi lebih lanjut, bicarakan dengan penyedia layanan Kesehatan Anda. Anda dapat bertanya kepada apoteker atau dokter Anda untuk informasi tentang Lylian® yang diresepkan.

Apa itu Lylian®?
Lylian® adalah serbuk liofilisasi untuk infus intravena yang digunakan untuk pendarahan tukak lambung.

Siapa yang tidak boleh menggunakan Lylian®?
Jangan menggunakan Lylian® jika Anda:

- Alergi terhadap Ilaprazole, atau komponen lain dalam obat ini atau benzimidazole. Lihat pada bagian akhir untuk daftar lengkap bahan-bahan dalam Lylian®
- Menggunakan salah satu obat berikut:
  Clopidogrel
  Atazanavir
  Nelfinavir
  Clarithromycin
  Amoxicillin
  Ketoconazole
  Itraconazole
  Tanyakan kepada dokter Anda, jika Anda tidak yakin apakah Anda menggunakan obat-obatan ini. JANGAN memulai pengobatan baru tanpa konsultasi dengan dokter Anda.
  Apa yang harus Saya tanyakan pada dokter Saya sebelum menggunakan Lylian®?
  Sebelum Anda menggunakan Lylian®, beri tahu dokter Anda jika Anda:

- Sedang menggunakan obat-obatan tertentu yang dapat mempengaruhi efektivitas Lylian®, seperti agen pelindung mukosa, termasuk Misoprostol, Sucralfate, Bismuth, dan lainnya.
- Menggunakan obat sebagai H2 receptor antagonists, seperti Cimetidine, Famotidine, Nizatidine, Ranitidine atau Romatidine, dan lainnya.
- Menggunakan obat PPI lainnya, seperti Lansoprazole, Omeprazole, Pantoprazole atau Rabeprazole dan antasida lainnya.
- Sedang menggunakan antikoagulan termasuk Heparin, Warfarin, Vitamin K antagonists dan lainnya, atau obat antiplatelet, Somatostatin dan analognya, NSAIDs, Corticosteroids.
- Memiliki gangguan hati atau ginjal.
- Mempunyai diagnosis tumor ganas di perut dan kerongkongan
- Hamil atau berencana untuk hamil, karena belum diketahui apakah Lylian akan membahayakan bayi Anda.
- Menyusui, karena belum diketahui apakah obat tersebut masuk ke dalam ASI atau dapat membahayakan bayi yang menyusui. Jangan gunakan obat ini tanpa memberi tahu dokter Anda jika Anda sedang menyusui bayi.

Beri tahu dokter Anda tentang semua obat yang Anda gunakan, termasuk resep dan obat bebas, vitamin dan suplemen herbal. Simpan daftar tersebut untuk ditunjukan kepada dokter Anda Ketika Anda mendapatkan pengobatan baru.

Bagaimana Lylian® digunakan?

- Gunakan Lylian® dengan benar seperti yang diperintahkan oleh dokter Anda.
- Dokter akan memberi tahu Anda berapa dosis dan kapan Lylian® perlu digunakan.
- Gunakan Lylian® selama dokter menganjurkan Anda menggunakannya.
- Jika overdosis hubungi dokter Anda atau pertolongan medis darurat terdekat.
- Lylian® harus disiapkan dengan cepat dan biasanya diberikan dalam waktu 30 menit melalu infus yang ditempatkan pada intravena.

Apa Kemungkinan Efek Samping dari Lylian®?

Lylian® dapat menyebabkan efek samping, termasuk:

- Peningkatan ALT dan AST
- Penurunan leukosit
- Peningkatan pada ALP, y-GT dan bilirubin total

Beri tahu dokter Anda jika Anda memiliki efek samping yang mengganggu atau tidak hilang. Ini tidak semua efek samping dari Lylian®. Untuk informasi lebih lanjut, tanyakan dokter Anda.

Bagaimana Saya harus menyimpan Lylian®?

Simpan Lylian® dalam wadah tertutup rapat dan terlindung dari cahaya dan simpan pada suhu tidak lebih dari 25°C.

Jauhkan Lylian® dari jangkauan anak-anak.

Apa kandungan Lylian®?
Zat aktif: Ilaprazole Sodium
Zat tambahan: Mannitol, Disodium Edetate, Sodium Hydroxide

Didaftarkan oleh:
PT Harsen Laboratories, Jakarta – Indonesia

HARUS DENGAN RESEP DOKTER
No.Reg.:

Diproduksi oleh:
Livzon (Group) Pharmaceutical Factory
Guangdong – China
Postal Code: 519045
Website: www.livzon.com.cn

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