

SOLOX

Lansoprazole 15 mg and 30 mg Capsules

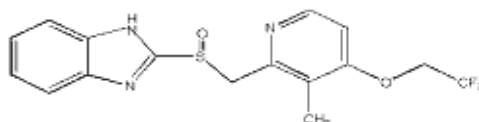
Name of the Medicine

SOLOX

Lansoprazole 15 mg and 30 mg Capsules

Description

Lansoprazole is a substituted benzimidazole. It is a white to slightly brownish crystalline, acid-labile powder, slightly soluble in ethanol and almost insoluble in water (0.033 mg/mL), but more soluble at higher pH. It is a chiral compound with one centre (-SO) and is present as a racemic mixture. Lansoprazole melts at 165.8 ° C with decomposition and has a pKa of 8.8. Lansoprazole is chemically identified as 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulphonyl]-1H-benzimidazole. CAS number 103577-45-3, molecular weight is 369.36 and the molecular formula is C₁₆H₁₄F₃N₃O₂S.



The capsules contain as excipients: neutral pellets (made of corn and saccharose), sodium lauryl sulphate, N-Methylglucamine, mannitol, hydroxypropyl methylcellulose, polyethylene glycol 6000, talc, polysorbate 80, titanium dioxide, Eudragit® (a methacrylic acid - ethyl acrylate copolymer). SOLOX 15 mg capsules contain gelatine, titanium dioxide and quinoline yellow in the capsule shell. SOLOX 30 mg capsules contain gelatine and titanium dioxide in the capsule shell.

Pharmacology

Mechanism of Action

Lansoprazole reduces gastric acid secretions by inhibiting the H⁺/K⁺-ATPase (proton pump) of the parietal cells in the gastric mucosa, the terminal phase of

acid secretion. The drug is effective in the treatment of acid-related disorders of the upper gastrointestinal tract.

A single dose of 30 mg lansoprazole inhibits stimulated acid secretion by approximately 80 %. Basal acid secretion and basal and stimulated secretion volumes are affected to a lesser degree.

After repeated dosing (for 7 days) 90 % inhibition of stimulated acid secretion is achieved. Despite its short elimination half-life, lansoprazole has a prolonged pharmacological action, providing effective suppression of gastric acid secretion over 24 hours.

When used in combination with the recommended antibiotics, SOLOX is associated with *H. pylori* eradication rates of up to 90 %.

Pharmacokinetics

Absorption

Lansoprazole is well absorbed and exhibits high bioavailability (80-90 %) following an oral dose. The bioavailability has been shown to be affected by the presence of food, however, acid inhibition (which is an endpoint for efficacy), as measured from sampling of gastric juice in healthy volunteers, is not significantly affected by food. It was shown in one study that morning dosing produced higher mean gastric pH values than afternoon dosing.

Distribution

Plasma protein binding is high (98 %) and is gender and concentration independent. Binding does not change as a result of multiple dosing. The plasma elimination half-life in healthy subjects ranges from 1 to 2 hours following a single dose or multiple doses. Peak plasma levels occur within 1.5 to 2.0 hours after dosing in these subjects.

After IV administration, the volume of distribution is 29 ± 4 L, total clearance is 31 ± 8 L/h and elimination half-life is 0.9 ± 0.44 h.

Elimination

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ¹⁴C-labelled lansoprazole showed that up to 50 % of the label was excreted in the urine, although unchanged drug does not appear to be excreted by this route; unchanged drug is eliminated, however, by biliary excretion.

Clinical Studies

Helicobacter Pylori

In clinical trials, the recommended dosage regimens were associated with *H. Pylori* eradication rates of up to 90 %. The best eradication rates were obtained with regimens which included clarithromycin. Trials, which used Lansoprazole 30 mg capsules in combination with only one antibiotic, resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux Oesophagitis

In two double-blind, placebo controlled multicentre studies (of 336 patients) examining the efficacy of lansoprazole 15 mg and 30 mg tablets in maintaining healed erosive reflux oesophagitis, lansoprazole was significantly superior to placebo in maintaining endoscopic and symptomatic freedom from disease. The time to median recurrence of either symptoms or endoscopic evidence of disease was less than 1 month for the placebo and greater than 12 months for 15 mg and 30 mg lansoprazole ($p \leq 0.001$). There was a slight trend for a better outcome with 30 mg lansoprazole although this was not statistically significant.

A study in 266 patients comparing lansoprazole 15 mg and 30 mg daily with ranitidine 300 mg twice daily, found both lansoprazole 15 mg and 30 mg increased the time to relapse and probability of no relapse in comparison to ranitidine. The percentage of patients who relapsed endoscopically during the 12-month maintenance period was 31 % in the lansoprazole 15 mg group, 20 % in the lansoprazole 30 mg group and 68 % in the ranitidine group. The difference between the lansoprazole groups and the ranitidine was apparent from the earliest time point in the study and maintained throughout the 12-month period. Comparison of treatment groups with regard to symptom control showed similar superiority of lansoprazole over ranitidine ($p \leq 0.001$ for each comparison).

A study in 882 patients comparing lansoprazole 15 mg and 30 mg daily with omeprazole 20 mg daily showed endoscopic remission rates (after 12 months) of 75 % with lansoprazole 15 mg daily, 88 % with lansoprazole 30 mg daily and 89 % with omeprazole 20 mg daily. The results demonstrate that lansoprazole 30 mg daily achieved significantly better remission rates compared to lansoprazole 15 mg daily and is of equal efficacy to omeprazole 20 mg daily.

The results of the 4 pivotal studies examining the use of lansoprazole in the long-term management of reflux oesophagitis are tabulated below:

Endoscopically Proven Relapse Rates at 12 Months

Study	Lansoprazole 15 mg I.d.	Lansoprazole 30 mg I.d.	Ranitidine 300 mg b.d.	Omeprazole 20 mg I.d.	Placebo
1 (n=163)	37 %	39 %	-	-	92 %
2 (n=184)	13 %	11 %	-	-	
3 (n=569)	31 %	20 %	68 %*	-	
4 (n=882)	25 %	12 %	-	11 %	

- not included in the study

* ($p \leq 0.001$) versus lansoprazole 15 mg and 30 mg

($p \leq 0.001$) versus omeprazole 20 mg and lansoprazole 30 mg

Duodenal Ulcer

In a study comparing lansoprazole 15 mg daily with placebo in 180 patients with endoscopically documented duodenal ulcer, the percentage of patients who remained healed after twelve months was significantly higher with lansoprazole than with placebo. Lansoprazole 15 mg was significantly superior to placebo in preventing endoscopic and symptomatic relapses of disease.

Duodenal Ulcer Recurrence Rates						
Treatment	Interval (months)					
	0-1	1-2	2-3	3-6	6-9	9-12
Placebo	20 %	36 %	52 %	60 %	60 %	62 %
Lansoprazole 15 mg	2 %*	8 %*	10 %*	14 %*	15 %*	17 %*

*($p < 0.001$) versus placebo

The maintenance studies discussed, using lansoprazole 15 mg and 30 mg did not extend beyond 12 months.

Indications

Healing and long-term management of reflux oesophagitis

Healing and maintenance therapy for patients with duodenal ulcer

Healing of benign gastric ulcer

Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H₂-receptor antagonists

The United States National Institute of Health have recommended that regimens to eradicate *H. pylori* in patients with peptic ulcer disease should contain both anti-secretory agents and anti-microbial agents (to which *H. pylori* has been demonstrated to be sensitive *in vivo*).

In an open, multicentre, comparative study in over 500 patients, 7 days treatment with lansoprazole 30 mg twice daily, in combination with the recommended antibiotics, was safe and efficacious in eradication of *H. Pylori* from patients with duodenal ulcer or gastritis and who tested positive for *H. Pylori*, with *H. Pylori* eradication rates of up to 90 %.

Contraindications

Hypersensitivity to lansoprazole or other proton pump inhibitors.

Severe hepatic impairment.

Precautions

General

As with other anti-ulcer therapies, the possibilities of malignancy should be excluded when a gastric ulcer is suspected, since treatment with lansoprazole may alleviate the symptoms of a malignancy and possibly delay its diagnosis.

Enterochromaffin-like (ECL) cell effects

Safety concerns of long term treatment relate to hypergastrinaemia and possible ECL effects. ECL cell hyperplasia and gastric carcinoid tumour were observed in animal studies (see PRECAUTIONS).

Human gastric biopsy specimens from patients treated with proton pump inhibitors have not detected ECL cell effects similar to those seen in rats. Gastric biopsies taken in all the long-term maintenance studies have revealed:

- A slight increase in mean endocrine cell count during 12 months maintenance treatment with lansoprazole 15 mg or 30 mg, observed in 3 of 4 studies. Cell density averages were slightly higher under 30 mg lansoprazole than under 15 mg lansoprazole once daily. These observations were reversible approximately 3 months after maintenance therapy stopped in two of the studies.
- Single cases of changes from normal to simple hyperplasia which persisted in one patient 3 months after discontinuation of treatment.

- For antral biopsies a greater mean gastrin-positive cell density and mean serotonin-positive cell density was found for lansoprazole 30 mg compared to lansoprazole 15 mg once daily.
- No evidence of carcinoid tumours or visible endocrine cell proliferation was seen in any patient for either fundus or antral biopsies.

(There are currently biopsy data on over 400 patients treated between 9 months and one year and over 230 patients treated for more than one year.)

Retinal atrophy

In animal studies, retinal atrophy was observed in Sprague Dawley rats dosed orally with lansoprazole. Retinal atrophy has not been found in mice, dogs, monkeys or humans. Mechanistic studies have indicated that the effect is specific to species dependent on hepatic synthesis of the amino acid taurine, which has a protective effect on the retina. Lansoprazole inhibits hepatic synthesis of taurine, however, humans obtain their taurine requirements from the diet.

Carcinogenicity, Mutagenicity, Impairment of fertility

In a 2 year carcinogenicity study in rats, oral doses of 5, 15 or 50 mg/kg/day, 5 days per week produced gastric ECL cell hyperplasia and carcinoid tumours in a dose-related manner in both male and female rats. The incidence of these effects was markedly higher in female rats. A "no effect" dose was not established for female rats. An increased incidence of benign Leydig cell tumours and testicular hyperplasia was also reported at dose levels of 15 mg/kg/day. Two repeat 2 year carcinogenicity studies in rats using doses ranging from 5-150 mg/kg/day, 7 days per week confirmed these findings. The effects of lansoprazole on human male fertility have not been evaluated.

In mice, a 78 week carcinogenicity study was performed at doses of 1.5, 5, 15 and 50 mg/kg/day, 5 days per week. No gastric ECL cell carcinoids were seen. In a repeat carcinogenicity study, mice were dosed with 15, 75, 150 or 300 mg/kg/day, 7 days a week. Terminal studies showed ECL cell hyperplasia, mucosal hyperplasia/hypertrophy and glandular dilatation and vacuolation at all dosages. Carcinoids were found in occasional animals receiving 15, 150 or 300 mg/kg/day.

Hypergastrinaemia secondary to prolonged hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumours develop.

Negative results were obtained in gene mutation assays and in an *in vivo* assay of chromosomal damage. *In vitro* assays of chromosomal damage showed evidence of chromosomal aberrations, though this may reflect cytotoxicity rather than genotoxic activity.

Use in Pregnancy

Pregnancy Category B3

Lansoprazole has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Reproductive studies conducted in pregnant rats and rabbits at oral doses up to 300 and 30 mg/kg/day, respectively, did not disclose any evidence of a teratogenic effect. A significant increase in foetal mortality was observed in the rabbit study at doses above 10 mg/kg/day. In rats a slight reduction in litter survival and weights was noted at doses above 100 mg/kg/day.

Use in Lactation

Animal studies indicate that lansoprazole is secreted into breast milk. There is no information on the secretion of lansoprazole into breast milk in humans. The use of lansoprazole during breast feeding should be avoided.

Use in Children

There is no experience with the use of lansoprazole in children.

Use in the Elderly

Dosage adjustment is not required in the elderly.

Other Precautions

Agents that elevate gastric pH may increase the already-present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

When using lansoprazole with antibiotics to eradicate *H. pylori*, it is recommended that prescribers refer to the approved product information for the antibiotics selected.

Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

Effects on Ability to Drive or Operate Machinery

Lansoprazole is likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

Interactions

Lansoprazole is metabolised in the liver and is a weak inducer of cytochrome P450. Therefore, there is the possibility of interaction with other drugs metabolised via this system e.g. theophylline. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

No clinically significant effects on plasma levels of warfarin, phenytoin (single IV doses only) and diazepam have been found.

The possibility of interaction between lansoprazole and low dose oral contraceptives cannot be excluded.

There is no evidence of an interaction between lansoprazole and non-steroidal anti-inflammatory drugs or antacids.

Co-administration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30 %. Therefore, lansoprazole should be taken at least 30 minutes prior to sucralfate.

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

Adverse effects

Lansoprazole is well tolerated. A low incidence of events has been reported during clinical trials in 7,867 patients treated with lansoprazole. These events, which are generally transient and self-limiting, include headache, diarrhoea, abdominal pain, dyspepsia, nausea, vomiting, dizziness, constipation, flatulence, rash, upper respiratory tract infections, urinary tract infections, arthralgia and myalgia. Dermatological reactions include urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of erythematous or bullous rashes including erythema multiforme. Cases of hair thinning and photosensitivity have also been reported. Other reported reactions include jaundice, hepatitis, interstitial nephritis (sometimes resulting in renal failure), anaphylaxis, wheezing, angioedema, bruising, purpura, petechiae, depression, peripheral oedema,

paraesthesia, blurred vision, taste disturbances, vertigo, confusion and hallucinations. Gynaecomastia and impotence may occur with long term use. During clinical trials a small number of patients developed abnormal liver function tests (predominantly gamma-GT) while on lansoprazole, however, routine monitoring of liver function tests is not required.

Isolated cases of blood dyscrasias, such as thrombocytopenia, leukopenia, neutropenia, agranulocytosis and pancytopenia have been reported, but a definite relationship to lansoprazole therapy has not been established.

Worldwide, there has been one report of acute colitis occurring in a 52-year-old male patient after treatment with 60 mg/day lansoprazole for six weeks.

As with any broad-spectrum antibiotic treatment, the risk of pseudomembranous colitis should be considered in patients using triple therapy for the eradication of *H. pylori*.

Dosage and Administration

Reflux oesophagitis: 30 mg lansoprazole once daily for 4 weeks. The majority of patients will be healed after the first course. For patients who have not fully healed within this time, a further 4 weeks treatment using the same dosage regimen is indicated. For long-term management, a maintenance dose of 15 mg or 30 mg once daily can be used dependent upon patient response.

Duodenal ulcer: 30 mg lansoprazole once daily for 4 weeks. For the prevention of relapse, the recommended maintenance dose is 15 mg once daily.

Gastric ulcer: 30 mg lansoprazole once daily for 8 weeks.

Eradication of *H. pylori*: Eradication of the infection is the single most important therapeutic intervention in patients with *H. pylori* positive peptic ulcer disease. The following combinations have been shown to be effective when used for 7 days: Solox 30 mg twice daily plus **two** of the following antibiotics: amoxicillin 1g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Long-term management: SOLOX capsules should only be used in certain situations including:

- In patients who have recurrent peptic ulceration where the pathogenesis of the ulcer is not related to *H. pylori* infection; or
- Where repeated eradication therapy is unsuccessful; or
- Patients who have a past history of perforation or bleeding from an ulcer.

Impaired hepatic and renal functions

Lansoprazole is metabolised substantially by the liver. The results of clinical trials in patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. However, no dose adjustment is necessary in these patients, although the daily dose should not exceed 30 mg.

There is no need to alter the dosage in patients with impaired renal function.

Overdosage

There is no information on the effect of acute overdosage. In case of overdose, supportive and symptomatic therapy should be initiated.

Doses of up to 180 mg/day for more than a year have been used to treat Zollinger Ellison Syndrome with no serious adverse effects.

Presentation

SOLOX 15 mg capsules: Hard gelatin capsules, opaque yellow cap and body, containing white or almost white spherical pellets.

SOLOX 30 mg capsules: Hard gelatin capsules, opaque white cap and body, containing white or almost white spherical pellets.

Storage

Store below 25 °C. Shelf life 3 years.

Pack quantities

SOLOX 15 mg capsules are available in blister packs containing 28 capsules.

SOLOX 30 mg capsules are available in blister packs containing 28 capsules. Also available in a starter pack of 7 capsules.

Medicine Classification

Prescription medicine

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