AUSTRALIAN PRODUCT INFORMATION – ZOTON FASTABS® (LANSOPRAZOLE)

1. NAME OF THE MEDICINE

Zoton® FasTabs 15 mg and 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zoton FasTabs contain 15 mg or 30 mg of lansoprazole.

Excipient(s) with known effect

Zoton FasTabs contains lactose monohydrate and aspartame.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

White to yellowish white circular, flat bevelled-edge oro-dispersible tablets speckled with orange to dark brown enteric-coated microgranules, with "15" or "30" debossed on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

1. Healing and long-term management of reflux oesophagitis.
2. Healing and long-term management for patients with duodenal ulcer.
3. Healing of benign gastric ulcer (see Section 4.2 Dose and method of administration).
4. Lansoprazole is also effective in patients with benign peptic lesions that do not respond to H_2-receptor antagonists.
5. Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer or chronic gastritis when used in combination with appropriate antibiotics (see Section 5.1 Pharmacological properties, **Clinical Trials**).
6. Relief of reflux-like and/or ulcer-like symptoms associated with acid-related dyspepsia.

Paediatric patients 6 to 17 years of age

1. Treatment of gastro-oesophageal reflux disease, including all grades of oesophagitis.
2. Healing of erosive oesophagitis.

4.2 Dose and method of administration

For oral administration.

Zoton FasTabs are strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the enteric-coated microgranules, which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water. The tablets must not be chewed.

The tablets should not be crushed or chewed (see Section 4.4 Special warnings and precautions for use). To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food.

Adults

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.

*Patients whose gastric or duodenal ulcer is not associated with ingestion of non-steroidal anti-inflammatory drugs require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation or on recurrence.

Acid-related dyspepsia

15 mg or 30 mg lansoprazole once daily for 2-4 weeks, depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

Eradication of H. pylori

The following combinations have been shown to be effective when used for 7 days:

30 mg lansoprazole twice daily plus **two** of the following antibiotics: amoxycillin 1 g twice daily, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily.

Paediatrics

Paediatric patients 6 to 11 years of age

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 (see Section 5.3 Preclinical safety data for nonclinical data).

Therapeutic indications	Classification	Posology
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 15 mg once daily for up to 12 weeks for children weighing ≤ 30 kg or 30 mg once daily for up to 12 weeks for children weighing > 30 kg.
Symptomatic Gastroesophageal reflux disease (s-GERD)		

Paediatric patients 12 to 17 years of age

In clinical studies, lansoprazole was not administered beyond 8 weeks in 12 to 17 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.

Therapeutic indications	Classification	Posology
Reflux esophagitis (Erosive esophagitis)	Short-term treatment	The recommended dose is 30 mg once daily for up to 8 weeks for erosive esophagitis
Symptomatic Gastroesophageal reflux disease (s-GERD)		The recommended dose is 15 mg once daily for up to 8 weeks for non-erosive GERD.

4.3 Contraindications

Hypersensitivity to lansoprazole, other proton pump inhibitors (PPIs) or any of the excipients in the tablets.

Severe hepatic impairment.

Lansoprazole should not be co-administered with atazanavir due to a significant reduction in atazanavir exposure.

4.4 Special warnings and precautions for use

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.

Similarly, the possibility of serious underlying disease such as malignancy should be excluded before treatment for dyspepsia commences, particularly in patients of middle age or older who have new or recently changed dyspeptic symptoms.

The granules in Zoton FasTabs are enteric coated. Therefore, the tablets should be sucked slowly and should not be crushed or chewed.

Use with caution in the following circumstances

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*. Proton pump inhibitor therapy may be associated with an increased risk of *Clostridium difficile* infection.

Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

PPIs, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive clinical guidelines and they should have an adequate intake of vitamin D and calcium.

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.

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 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.

Acute Tubulointerstitial Nephritis (TIN)

Acute TIN has been observed in patients taking PPIs including lansoprazole. Acute TIN may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue lansoprazole if acute TIN develops.

Hypomagnesaemia

Hypomagnesaemia, 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 hypomagnesaemia 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 hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (undesirable effects).

Subacute Cutaneous Lupus Erythematosus (SCLE)

Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). 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 healthcare professional should consider stopping the product.

Use in hepatic impairment Lansoprazole is metabolised substantially by the liver. The results of clinical trials in adult patients with liver disease indicate that the metabolism of lansoprazole is prolonged in patients with severe hepatic impairment. Consider dose adjustment in patients with severe hepatic impairment.

Use in renal impairment

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

Use in the elderly

Dosage adjustment is not required in the elderly.

Paediatric use

See Section 4.2 Dose and method of administration – Paediatrics.

There is insufficient experience to recommend the use of lansoprazole in paediatric patients with hepatic or renal impairment.

Effects on laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

4.5 Interactions with other medicines and other forms of 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, phenytoin, carbamazepine and warfarin. Patients receiving such drugs concomitantly with lansoprazole should be monitored to determine if any dosage adjustment is necessary.

There have been isolated cases of a suspected drug interaction with warfarin, but a definitive relationship to lansoprazole therapy has not been established.

No clinically significant effects on plasma levels of non-steroidal anti-inflammatory drugs, phenytoin (single IV doses only) and diazepam have been found.

Concomitant administration of lansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure to lansoprazole. Inducers of CYP2C19 would likely decrease the systemic exposure to lansoprazole. The possibility of interaction between lansoprazole and low-dose oral contraceptives cannot be excluded.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Similarly, antacids may also reduce the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least an hour prior to sucralfate or antacid administration.

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).

Coadministration of PPIs in healthy subjects and in transplant patients receiving mycophenolate mofetil has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving PPIs and mycophenolate mofetil. Use lansoprazole with caution in transplant patients receiving mycophenolate mofetil.

Concomitant use with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite, possible leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Lansoprazole, and other PPIs, should not be co-administered with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH (e.g. atazanavir and nelfinavir), due to significant reduction in their bioavailability. The decreased systemic concentration of the HIV protease inhibitor may result in a loss of therapeutic effect and the development of HIV resistance.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See Section 5.3 Preclinical safety data.

Use in pregnancy – Pregnancy Category B3

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 fetal 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.

There are insufficient data to recommend the administration of lansoprazole during pregnancy. Lansoprazole should not be used during pregnancy, unless the benefit clearly outweighs the potential risk to the fetus.

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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Zoton is well-tolerated, with adverse events generally being mild and transient.

Nervous system disorders

Headache and dizziness.

Rarely, paraesthesia and taste disturbances.

Psychiatric disorders

Depression, confusion and hallucinations.

Gastrointestinal disorders

Diarrhoea, constipation, abdominal pain, dyspepsia, nausea, vomiting, flatulence, and dry or sore mouth or throat.

Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Rarely, cases of colitis (macroscopic and microscopic) have been reported. In severe and/or protracted cases of diarrhoea, discontinuation of therapy should be considered. In the majority of cases symptoms resolve on discontinuation of therapy.

Infections and infestations

Upper respiratory tract infections, urinary tract infections.

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*.

Hepatobiliary disorders

Abnormal liver function test values, elevation of aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (γ-GTP).

Rarely, jaundice or hepatitis, have been reported. However, routine monitoring of liver function tests is not required.

Skin and subcutaneous tissue disorders

Skin rashes, urticaria and pruritus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and erythematous or bullous rashes including cutaneous lupus erythematosus and erythema multiforme. Cases of hair thinning and photosensitivity have also been reported.

Immune system disorders

Angioedema, wheezing, and very rarely, anaphylactic reaction.

Renal and urinary disorders

Cases of Tubulointerstitial Nephritis TIN have been reported which have sometimes resulted in renal failure.

Metabolism and nutrition disorders

Hypomagnesaemia has been reported rarely. Hypocalcaemia and hypokalaemia have been reported, which may be related to the occurrence of hypomagnesaemia (see section 4.4 Special Warnings and Precautions). There have been isolated reports of hyponatraemia.

Blood and lymphatic system disorders

Haematological effects (thrombocytopenia, agranulocytosis, eosinophilia, leucopoenia, neutropenia and pancytopenia) have occurred rarely. Bruising, purpura and petechiae have also been reported.

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia.

Eye disorders

Blurred vision.

Ear and labyrinth disorders

Vertigo.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial pneumonia, but a definitive relationship to lansoprazole therapy has not been established.

Reproductive system and breast disorders

Gynaecomastia and erectile dysfunction have been reported rarely.

Injury, poisoning and procedural complications

Fracture of the hip, wrist or spine has been reported.

General disorders and administration site conditions

Fatigue, malaise, peripheral oedema.Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no information on the effect of acute overdosage. In a 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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, Zoton is associated with *H. pylori* eradication rates of up to 90%.

Clinical trials

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 Zoton in combination with only one antibiotic resulted in significantly lower eradication rates. Therefore, such regimens are not recommended.

Reflux oesophagitis

Paediatrics

In an open-label, U.S. multicentre study, 66 children, 1 to 11 years of age, with GORD were assigned to receive an initial dose of either lansoprazole 15 mg capsules once daily, if the body weight was <30 kg, or lansoprazole 30 mg capsules once daily, if the body weight was >30 kg, administered for 8 to 12 weeks. The lansoprazole dose was increased up to 60 mg daily in some children after 2 weeks of treatment.

Erosive and Non Erosive GORD	**Final Visit[a] % (n/N)**
Erosive GORD healing rate	100% (27/27)
Improvement in overall GORD symptoms	76% (47/62[b])

[a]At week 8 or 12. [b]No data were available for 4 children.

Treatment with lansoprazole also demonstrated significant reduction in frequency and severity of GORD symptoms ($p<0.001$).

In a double blind, U.S. multicentre study, 63 patients 12 to 17 years of age with proven GORD were randomised to receive either lansoprazole 15 mg once daily or 30 mg once daily for five days. Subjects in both groups demonstrated improvement in symptoms of reflux disease. A reduction in heartburn severity was shown to be statistically significant for patients treated with

either 15 mg or 30 mg lansoprazole. The majority of patients (69% for lansoprazole 15 mg once daily and 74% for lansoprazole 30 mg once daily) reported that their reflux symptoms were better after treatment.

Adults

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 ($p < 0.001$ 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 once daily	Lansoprazole 30 mg once daily	Ranitidine 300 mg twice daily	Omeprazole 20 mg once daily	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

	Interval (months)					
Treatment	**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%*

*($p \leq 0.001$) versus placebo

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

Acid-related dyspepsia

The efficacy of lansoprazole 15-30 mg daily has been examined in a total of 531 patients, compared with ranitidine (n=171), omeprazole (n=281) and placebo (n=138).

The efficacy of lansoprazole (30 mg mane) was compared to ranitidine (150 mg bd) for the treatment of acid-related dyspepsia in a double-blind, parallel, 4-week study. The results are presented in the following table.

Number of Patients with No Symptoms						
	Week 2			**Week 4**		
	Lansoprazole	**Ranitidine**	**P value**	**Lansoprazole**	**Ranitidine**	**P value**
No symptoms	95/171 (55%)	56/171 (33%)	0.001	95/137 (69%)	63/145 (44%)	0.001
No DT.H	91/138 (66%)	68/139 (49%)	0.006	89/111 (80%)	66/120 (55%)	0.001
No NT.H	89/128 (69%)	64/124 (52%)	0.005	86/103 (83%)	68/106 (64%)	0.003
No DT.EP	78/127 (61%)	62/140 (45%)	0.007	72/100 (72%)	71/120 (60%)	0.06
No NT.EP	79/115 (68%)	59/120 (50%)	0.004	74/91 (81%)	67/104 (65%)	0.01

DT = Daytime H = Heartburn
NT = Night-time EP = Epigastric Pain

There was also a significant difference in the usage of "rescue" antacid treatment in the two groups, with 67% of the lansoprazole group taking antacids in the first two weeks of treatment compared with 83% of the ranitidine group (p=0.001).

In patients with symptoms of ulcer-like and reflux-like dyspepsia, lansoprazole 15 mg mane was compared to omeprazole 10 mg mane for a 4-week period in a double-blind, parallel study. In the primary efficacy analyses in the intent to treat population, the study revealed that more patients were free of overall primary symptoms of dyspepsia in the lansoprazole-treated group compared to the omeprazole-treated group (p=0.007 and 0.078 respectively).

% of Patients with No Symptoms (heartburn and epigastric pain): ITT Analysis

	Treatment	**Symptom Free Patients n (%)**		**P value**
		Lansoprazole	**Omeprazole**	
Overall Primary Symptoms	2 weeks	150 (53%)	115 (41%)	0.007
	4 weeks	167 (59%)	143 (51%)	0.078
Relief of Daytime Heartburn	2 weeks	164 (70%)	131 (58%)	0.011
	4 weeks	163 (70%)	145 (64%)	0.28
Relief of Night-time Heartburn	2 weeks	140 (69%)	132 (63%)	0.23
	4 weeks	146 (72%)	144 (68%)	0.53
Relief of Daytime Epigastric Pain	2 weeks	129 (63%)	88 (46%)	0.001
	4 weeks	137 (67%)	114 (60%)	0.17
Relief of Night-time Epigastric Pain	2 weeks	108 (61%)	91 (52%)	0.11
	4 weeks	113 (64%)	104 (60%)	0.46

Non-ulcer dyspepsia

A randomised, double-blind parallel study 15 mg lansoprazole mane was compared to placebo in 269 patients suffering from non-ulcer dyspepsia. In the intent-to-treat population the healing rate was 81/131 (61.8%) in the lansoprazole group after 2-3 weeks treatment, compared to 61/138 (44.2%) in the placebo group (p=0.005). In the 3-month follow-up period, the recurrence of non-ulcer dyspepsia symptoms was reported by 32/86 (37.2%) patients in the lansoprazole group and by 29/79 (36.7%) in the placebo group (p=1.0). Healing was defined

as the percentage of patients with no heartburn or acid regurgitation, as well as no nausea and vomiting and a reduction in the Visual Analogue Scale value of ≤ 20% during the last 5 days of treatment.

5.2 Pharmacokinetic properties

Adults

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 a.m. dosing produced higher mean gastric pH values than p.m. 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.

Metabolism/Excretion

Following absorption, lansoprazole is extensively metabolised and the metabolites are excreted by both the renal and biliary route. A study with ^{14}C-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.

Paediatric patients 1 to 11 years of age

The pharmacokinetics of lansoprazole were studied in paediatric patients with gastro-oesophageal reflux disease (GORD) aged 1 to 11 years, with lansoprazole capsule doses of 15 mg once daily for subjects weighing <30 kg and 30 mg once daily for subjects weighing >30 kg. Lansoprazole pharmacokinetics in these paediatric patients were similar to those previously observed in healthy adult subjects. The mean C_{max} and AUC values were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in this study.

Paediatric patients 12 to 17 years of age

In a study of paediatric patients aged 12 to 17 years with GORD, the pharmacokinetics of lansoprazole were shown to be similar to those previously observed in healthy adult subjects. No statistically significant differences were observed between doses for T_{max}, $t_{½}$ or natural logarithms of dose-normalised C_{max} and AUC_{0-24}. None of the selected covariates (body weight, age and gender) had any statistically significant effect on lansoprazole T_{max} or the natural logarithms of dose normalised C_{max} and AUC_{0-24}.

5.3 Preclinical safety data

Genotoxicity

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.

Carcinogenicity

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.

Juvenile Animal Studies

In an 8-week juvenile rat study, changes in male reproductive tissue (testes and epididymis) and heart (cardiac valve thickening) occurred at approximately 6-fold and 11-fold the expected human exposure, respectively, based on AUC (75-fold and 150-fold the expected human exposure based on body surface area). The findings reversed or trended towards reversibility after a 4-week drug-free recovery period. In a follow-up lansoprazole developmental sensitivity study, juvenile rats younger than postnatal Day 21 (age equivalent to approximately 2 years in humans) were more sensitive to the development of heart valve thickening, with valve thickening occurring at lower exposure (approximately 4-fold the expected human exposure based on AUC) in animals dosed starting at postnatal Day 14 (age equivalent to approximately 1 year in humans).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The gastro-resistant microgranules contain the excipients; lactose monohydrate, microcrystalline cellulose, magnesium carbonate hydrate, low-substituted hyprolose, hyprolose, hypromellose, titanium dioxide, purified talc, mannitol, methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent, polyacrylate dispersion 30 per cent, macrogol 8000, citric acid, glyceryl monostearate, polysorbate 80, triethyl citrate, iron oxide yellow (E172) and iron oxide red (E172).

Other excipients contained in the tablets are crospovidone, magnesium stearate, strawberry flavour and aspartame.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Zoton FasTabs should be stored below 25 ºC.

6.5 Nature and contents of container

Supplied in blister packs of 7 or 28 tablets.

6.6 Special precautions for disposal

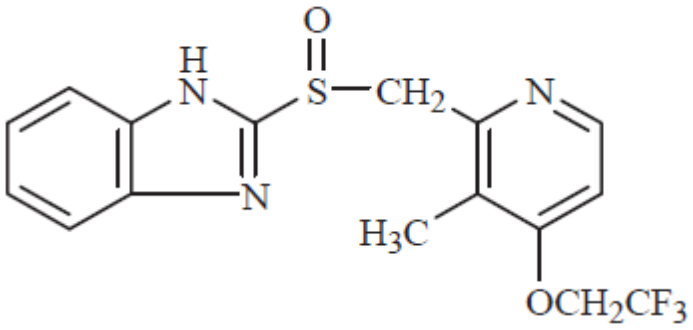
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Non-proprietary name: lansoprazole

The structural formula of lansoprazole is shown below:



Chemical name: 2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulphinyl]-1H-benzimidazole.

Molecular formula: $C_{16}H_{14}F_3N_30_2S$

Molecular weight: MW 369.36

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.

CAS number

CAS Registry Number: CAS No. 103577-45-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000

Toll Free Number: 1800 675 229.
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Zoton FasTabs 15 mg and 30 mg tablets: 14 January 2009.

10. DATE OF REVISION

15 April 2021

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Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of hypocalcaemia and hypokalaemia to existing hypomagnesaemia warning. References to Interstitial nephritis amended to Tubulointerstitial Nephritis (TIN).
4.8	Addition of hypokalaemia, hypocalcaemia and hyponatraemia adverse effects. Addition of DRESS adverse effect.