Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zoton FasTab 15mg Oro-dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oro-dispersible tablet contains 15mg of lansoprazole.

Excipients: Each tablet contains 15 mg of lactose and 4.5 mg of aspartame
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.
Product imported from the UK and Italy:
White to yellowish white, circular flat beveled-edge oro-dispersible tablet with “15” debossed on one side. Each oro-dispersible tablet contains orange to dark brown microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of duodenal and gastric ulcer
Treatment of reflux oesophagitis
Prophylaxis of reflux oesophagitis
Eradication of Helicobacter pylori (H. pylori) concurrently given with appropriate antibiotic therapy for treatment of H.pylori-associated ulcers
Treatment of NSAID-associated benign gastric and duodenal ulcers in patients requiring continued NSAID treatment
Prophylaxis of NSAID-associated gastric ulcers and duodenal ulcers in patients at risk (see section 4.2) requiring continued therapy
Symptomatic gastroesophageal reflux disease
Zollinger-Ellison syndrome.

4.2 Posology and method of administration

For optimal effect, Zoton FasTab should be taken once daily in the morning, except when used for H. pylori eradication when treatment should be twice a day, once in the morning and once in the evening. Zoton FasTab should be taken at least 30 minutes before food (see section 5.2). Zoton FasTab is strawberry flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing gastro-resistant microgranules which are swallowed with the patient's saliva. Alternatively, the tablet can be swallowed whole with a drink of water.
The orodispersible tablets can be dispersed in a small amount of water and administered via a naso-gastric tube or oral syringe.

Treatment of duodenal ulcer:
The recommended dose is 30 mg once daily for 2 weeks. In patients not fully healed within this time, the medication is continued at the same dose for another two weeks.

Treatment of gastric ulcer:
The recommended dose is 30 mg once daily for 4 weeks. The ulcer usually heals within 4 weeks, but in patients not fully healed within this time, the medication may be continued at the same dose for another 4 weeks.

Reflux oesophagitis:
The recommended dose is 30 mg once daily for 4 weeks. In patients not fully healed within this time, the treatment may be continued at the same dose for another 4 weeks.

Prophylaxis of reflux oesophagitis:
15 mg once daily. The dose may be increased up to 30 mg daily as necessary.

Eradication of Helicobacter pylori:
When selecting appropriate combination therapy consideration should be given to official local guidance regarding bacterial resistance, duration of treatment, (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.
The recommended dose is 30 mg of Zoton FasTab twice daily for 7 days in combination with one of the following:
clarithromycin 250-500 mg twice daily + amoxicillin 1 g twice daily
clarithromycin 250 mg twice daily + metronidazole 400-500 mg twice daily
The H. pylori eradication results obtained when clarithromycin is combined with either amoxicillin or metronidazole give rates of up to 90%, when used in combination with Zoton FasTab.
Six months after successful eradication treatment, the risk of re infection is low and relapse is therefore unlikely.
Use of a regimen including lansoprazole 30 mg twice daily, amoxicillin 1 g twice daily and metronidazole 400-500 mg twice daily has also been examined. Lower eradication rates were seen using this combination than in regimens involving clarithromycin. It may be suitable for those who are unable to take clarithromycin as part of an eradication therapy, when local resistance rates to metronidazole are low.

Treatment of NSAID associated benign gastric and duodenal ulcers in patients requiring continued NSAID treatment:
30 mg once daily for four weeks. In patients not fully healed the treatment may be continued for another four weeks. For patients at risk or with ulcers that are difficult to heal, a longer course of treatment and/or a higher dose should probably be used.

Prophylaxis of NSAID associated gastric and duodenal ulcers in patients at risk (such as age> 65 or history of gastric or duodenal ulcer) requiring prolonged NSAID treatment:
15 mg once daily. If the treatment fails the dose 30 mg once daily should be used.

Symptomatic gastro-oesophageal reflux disease:
The recommended dose is 15 mg or 30 mg daily. Relief of symptoms is obtained rapidly. Individual adjustment of dosage should be considered. If the symptoms are not relieved within 4 weeks with a daily dose of 30 mg, further examinations are recommended.

Zollinger-Ellison syndrome:
The recommended initial dose is 60 mg once daily. The dose should be individually adjusted and the treatment should be continued for as long as necessary. Daily doses of up to 180 mg have been used. If the required daily dose exceeds 120 mg, it should be given in two divided doses.

Impaired hepatic or renal function:
There is no need for a dose adjustment in patients with impaired renal function.
Patients with moderate or severe liver disease should be kept under regular supervision and a 50% reduction of the daily dose is recommended (see section 4.4 and 5.2).

Elderly:
Due to reduced clearance of lansoprazole in the elderly an adjustment of dose may be necessary based on individual requirements. A daily dose of 30 mg should not be exceeded in the elderly unless there are compelling clinical indications.

Children:
The use of Zoton FasTab is not recommended in children as clinical data are limited (see also section 5.2.)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Lansoprazole should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

In common with other anti-ulcer therapies, the possibility of malignant gastric tumour should be excluded when treating a gastric ulcer with lansoprazole because lansoprazole can mask the symptoms and delay the diagnosis.
Lansoprazole should be used with caution in patients with moderate and severe hepatic dysfunction (see sections 4.2 and 5.2).
Decreased gastric acidity due to lansoprazole might be expected to increase gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with lansoprazole may lead to a slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.
In patients suffering from gastro-duodenal ulcers, the possibility of H. pylori infection as an etiological factor should be considered.
If lansoprazole is used in combination with antibiotics for eradication therapy of H.pylori, then the instructions for the use of these antibiotics should also be followed.
Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment and a thorough risk/benefit assessment should regularly be performed in these patients.
Very rarely cases of colitis have been reported in patients taking lansoprazole. Therefore, in the case of severe and/or persistent diarrhoea, discontinuation of therapy should be considered.
The treatment for the prevention of peptic ulceration of patients in need of continuous NSAID treatment should be restricted to high risk patients (e.g. previous gastrointestinal bleeding, perforation or ulcer, advanced age, concomitant use of medication known to increase the likelihood of upper GI adverse events [e.g. corticosteroids or anticoagulants], the presence of a serious co-morbidity factor or the prolonged use of NSAID maximum recommended doses).
As Zoton FasTab contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Proton pump inhibitors, 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 recognized risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like lansoprazole for at least three months, and in most cases for a year. Serious manisfestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of lansoprazole on other drugs

Medicinal products with pH dependent absorption

Lansoprazole may interfere with the absorption of drugs where gastric pH is critical to bioavailability.

Atazanavir:

A study has shown that co-administration of lansoprazole (60 mg once daily) with atazanavir 400 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 90% decrease in AUC and Cmax). Lansoprazole should not be co-administered with atazanavir (see section 4.3).

Ketoconazole and itraconazole:

The absorption of ketoconazole and itraconazole from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of lansoprazole may result in sub-therapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided.

Digoxin:

Co-administration of lansoprazole and digoxin may lead to increased digoxin plasma levels.

The plasma levels of digoxin should therefore be monitored and the dose of digoxin adjusted if necessary when initiating and ending lansoprazole treatment.

Medicinal products metabolised by P450 enzymes

Lansoprazole may increase plasma concentrations of drugs that are metabolised by CYP3A4. Caution is advised when combining lansoprazole with drugs which are metabolised by this enzyme and have a narrow therapeutic window.

Theophylline:

Lansoprazole reduces the plasma concentration of theophylline, which may decrease the expected clinical effect at the dose. Caution is advised when combining the two drugs.

Tacrolimus:

Co-administration of lansoprazole increases the plasma concentrations of tacrolimus (a CYP3A and P-gp substrate). Lansoprazole exposure increased the mean exposure of tacrolimus by up to 81%. Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with lansoprazole is initiated or ended.

Medicinal products transported by P-glycoprotein

Lansoprazole has been observed to inhibit the transport protein, P-glycoprotein (P-gp) in vitro. The clinical relevance of this is unknown.

Effects of other drugs on lansoprazole:

Drugs which inhibit CYP2C19

Fluvoxamine:

A dose reduction may be considered when combining lansoprazole with the CYP2C19 inhibitor fluvoxamine. A study shows that the plasma concentrations of lansoprazole increase up to 4-fold.

Drugs which induces CYP2C19 and CYP3A4

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin, and St John's wort (Hypericum perforatum) can markedly reduce the plasma concentrations of lansoprazole.

Others

Sucralfate/Antacids:

Sucralfate/Antacids may decrease the bioavailability of lansoprazole. Therefore lansoprazole should be taken at least 1 hour after taking these drugs.

No clinically significant interactions of lansoprazole with nonsteroidal anti-inflammatory drugs have been demonstrated, although no formal interactions studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy:
For lansoprazole no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Therefore, the use of lansoprazole during pregnancy is not recommended.

Lactation:
It is not known whether lansoprazole is excreted in human breast milk. Animal studies have shown excretion of lansoprazole in milk.
A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with lansoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of lansoprazole therapy to the woman.

4.7 Effects on ability to drive and use machines

Adverse drug reactions such as dizziness, vertigo, visual disturbances and somnolence may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effects

Frequencies are defined as common > 1/100, < 1/10); uncommon > 1/1,000, < 1/100); rare >1/10,000, <1/1,000); very rare (<1/10,000).

	Common	Uncommon	Rare	Very Rare	Unknown
Blood and lymphatic system disorders		Thrombocytopenia, eosinophilia, leucopenia	Anaemia	Agranulocytosis, pancytopenia	
Psychiatric disorders		Depression	Insomnia, hallucination, confusion		
Nervous system disorders	Headache, dizziness		Restlessness, vertigo, paresthesia, somnolence, tremor		
Eye disorders			Visual disturbance		
Gastrointestinal disorders	Nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence, dry mouth or throat		Glossitis, candidiasis of the oesophagus, pancreatitis, taste disturbances	Colitis, stomatitis	
Hepatobiliary	Increase in		Hepatitis,		

disorders	liver enzyme levels		jaundice		
Skin and subcutaneous tissue disorders	Urticaria, itching, rash		Petechiae, purpura, hair loss, erythema multiforme, photosensitivity	Steven-Johnson syndrome, toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)			
Renal and urinary disorders			Interstitial nephritis		
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Fatigue	Oedema	Fever, hyperhidrosis, angioedema, anorexia, mpotence	Anaphylactic shock	
Investigations				Increase in cholesterol and triglyceride levels, hyponatremia	
Metabolism and nutritional disorders					Hypomagnesaemia. [See Special warnings and precautions for use (4.4)]

4.9 Overdose

The effects of overdose on lansoprazole in humans are not known (although the acute toxicity is likely to be low) and, consequently, instruction for treatment cannot be given. However, daily doses of up to 180 mg of lansoprazole orally and up to 90 mg of lansoprazole intravenously have been administered in trials without significant undesirable effects. Please refer to section 4.8 for possible symptoms of lansoprazole overdose.
In the case of suspected overdose the patient should be monitored. Lansoprazole is not significantly eliminated by haemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, *ATC code*: A02BC03
Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage of gastric acid formation by inhibiting the activity of H^+/K^+ ATPase of the parietal cells in the stomach. The inhibition is dose-dependent and reversible, and the

effect applies to both basal and stimulated secretion of gastric acid. Lansoprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulphydryl group of H^+/K^+ATPase causing inhibition of the enzyme activity.

Effect on gastric acid secretion:

Lansoprazole is a specific inhibitor of the parietal cell proton pump. A single oral 30 mg dose of lansoprazole inhibits pentagastrin-stimulated gastric acid secretion by about 80%. After repeated daily administration for sevendays, about 90% inhibition of gastric acid secretion is achieved. It has a corresponding effect on the basal secretion of gastric acid. A single oral dose of 30 mg reduces basal secretion by about 70%, and the patients' symptoms are consequently relieved starting from the very first dose. After eight days of repeated administration the reduction is about 85%. A rapid relief of symptoms is obtained by one oro-dispersible tablet (30 mg) daily, and most patients with duodenal ulcer recover within 2 weeks, patients with gastric ulcer and reflux oesophagitis within 4 weeks. By reducing gastric acidity, lansoprazole creates an environment in which appropriate antibiotics can be effective against H. pylori.

5.2 Pharmacokinetic properties

Lansoprazole is a racemate of two active enantiomers that are biotransformed into the active form in the acidic environment of the parietal cells. As lansoprazole is rapidly inactivated by gastric acid, it is administered orally in enteric-coated form(s) for systemic absorption.

Absorption and distribution
Lansoprazole exhibits high (80-90%) bioavailability with a single dose. Peak plasma levels occur within 1.5 to 2.0 hours. Intake of food slows the absorption rate of lansoprazole and reduces the bioavailability by about 50%. The plasma protein binding is 97%.
Studies have shown that oro-dispersible tablets dispersed in a small amount of water and given via syringe directly into the mouth or administered via naso-gastric tube result in equivalent AUC compared to the usual mode of administration.

Metabolism and elimination
Lansoprazole is extensively metabolised by the liver and the metabolites are excreted by both the renal and biliary route. The metabolism of lansoprazole is mainly catalysed by the enzyme CYP2C19. The enzyme CYP3A4 also contributes to the metabolism. The plasma elimination half-life ranges from 1 to 2 hours following single or multiple doses in healthy subjects. There is no evidence of accumulation following multiple doses in healthy subjects. Sulphone, sulphide and 5-hydroxyl derivatives of lansoprazole have been identified in plasma. These metabolites have very little or no antisecretory activity.
A study with ^{14}C labelled lansoprazole indicated that approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the faeces.

Pharmacokinetics in elderly patients
The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Peak plasma levels were not increased in the elderly.
Pharmacokinetics in paediatric patients
The evaluation of the pharmacokinetics in children aged 1 –17 years of age showed a similar exposure as compared to adults with doses of 15 mg for those below 30 kg of weight and 30 mg for those above. The investigation of a dose of 17 mg/m^2 body surface or 1 mg/kg body weight also resulted in comparable exposure of lansoprazole in children aged 2-3 months up to one year of age compared to adults.
Higher exposure to lansoprazole in comparison to adults has been seen in infants below the age of 2-3 months with doses of both 1.0 mg/kg and 0.5 mg/kg body weight given as a single dose.

Pharmacokinetics in hepatic insufficiency
The exposure of lansoprazole is doubled in patients with mild hepatic impairment and much more increased in patients with moderate and severe hepatic impairment.

CYP2C19 poor metabolisers
CYP2C19 is subject to genetic polymorphism and 2-6 % of the population, called poor metabolisers (PMs), are homozygote for a mutant CYP2C19 allele and therefore lacks a functional CYP2C19 enzyme. The exposure of lansoprazole is several-fold higher in PMs than in extensive metabolisers (EMs).

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction or genotoxicity.
In two rat carcinogenicity studies, lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids associated with hypergastrinaemia due to inhibition of acid secretion. Intestinal metaplasia was also observed, as were Leydig cell hyperplasia and benign Leydig cell tumours. After 18 months of treatment retinal atrophy was observed. This was not seen in monkeys, dogs or mice.
In mouse carcinogenicity studies dose-related gastric ECL cell hyperplasia developed as well as liver tumours and adenoma of rete testis.
The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Magnesium carbonate
Low-substituted hydroxypropyl cellulose
Hydroxypropyl cellulose
Hypromellose
Titanium dioxide
Talc
Mannitol (E421)
Methacrylic acid – ethyl acrylate copolymer (1:1) 30 per cent
Polyacrylate dispersion 30 per cent
Macrogol 8000
Glyceryl monostearate
Polysorbate 80
Triethyl citrate
Citric acid anhydrous
Crospovidone
Magnesium stearate
Aspartame (E951)
Strawberry flavour
Iron oxide red and yellow (E172).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Aluminium blisters in an overlabelled carton containing 14 or 28 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare
Unit 4, Bradfield Road
Ruislip
Middlesex
HA4 0NU
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/78/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th May 2009

10 DATE OF REVISION OF THE TEXT

June 2012