# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

ByLans 30 mg Gastro-resistant Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains lansoprazole 30 mg.
Excipients:
Each capsule contains 129.6 mg sucrose (in sugar spheres)

For a full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard.

Size 1 , white cap marked with ‘L’ and white body marked with ‘30’, containing white to beige gastro-resistant micropellets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Treatment of duodenal and/or benign gastric ulcer.

Treatment and prophylaxis of reflux oesophagitis.

Symptomatic Gastroesophageal Reflux Disease (GORD).

Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and relief of symptoms in patients requiring continued NSAID treatment.

Treatment of Zollinger-Ellison syndrome.

Eradication of *Helicobacter pylori* concurrently given with appropriate antibiotic therapy and prevention of relapse of peptic ulcers in patients with *H.pylori* associated ulcers.

### 4.2 Posology and method of administration

For optimal effect, lansoprazole 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. Lansoprazole should be taken at least 30 minutes before food (see section 5.2). Capsules should be swallowed whole with liquid.

The capsules should be swallowed whole. Do not crush or chew.

Dosage:

Treatment of duodenal ulcer: the recommended dose is lansoprazole 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 benign gastric ulcer: the recommended dose is lansoprazole 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 lansoprazole 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: lansoprazole 15 mg once daily. The dose may be increased up to 30 mg daily as necessary.

Symptomatic Gastroesophageal Reflux Disease: the recommended dose is lansoprazole 15 or 30 mg once 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.

Treatment of NSAID-associated benign gastric and duodenal ulcers and relief of symptoms: lansoprazole 30mg once daily for 4 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, the higher dose and/or the longer treatment duration should probably be used.

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

Zollinger-Ellison Syndrome: the recommended initial dose is lansoprazole 60 mg once daily. The dosage should then be adjusted individually. Treatment should be continued for as long as clinically indicated. Daily doses of up to 180 mg have been used. For patients who require 120 mg or more per day, the dose should be divided and administered twice daily.

Helicobacter pylori eradication:
When selecting appropriate combination therapy consideration should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance, duration of treatment, (most commonly 7 days but sometimes up to 14 days) and the appropriate use and prescription of antibacterial agents.

The recommended dose is 30 mg lansoprazole 2 times daily for one week in combination with one of the following three combinations:

A) Amoxicillin 1g twice daily + clarithromycin 250-500 mg twice daily,
B) Clarithromycin 250 mg twice daily + metronidazole 400-500 mg twice daily,
C) Amoxicillin 1g twice daily + metronidazole 400-500 mg twice daily.

H. pylori eradication rates of up to 90%, are obtained when clarithromycin is combined with lansoprazole and amoxicillin or metronidazole.

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.

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

Children: The use of lansoprazole is not recommended in children as clinical data are limited. Treatment of small children below one year of age should be avoided as available data have not shown beneficial effects in the treatment of gastro-oesophageal reflux.

Impaired Hepatic and 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).

There is no need to alter the dosage in patients with mild impairment of hepatic function or impaired renal function.

## 4.3 Contraindications

The use of lansoprazole is contra-indicated in patients with a history of hypersensitivity to any of the ingredients of lansoprazole capsules.

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 symptoms may be masked and diagnosis delayed.
Lansoprazole should be used with caution in patients with moderate and severe hepatic dysfunction. (See Section 4.2 and 5.2).

Decreased gastric acidity due to lansoprazole might be expected to increases 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 aetiological factor should be considered. If lansoprazole, in combination with antibiotics, is used for eradication therapy of *H.pylori*, then instructions for the use of these antibiotics should also be followed.

Because of limited safety data for patients on maintenance treatment for longer than one 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).

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 manifestations 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.

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 recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of 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.

This product contains sucrose and therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

## 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 subtherapeutic 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: Coadministration 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 lanzoprazole 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:
Drugs which inhibit CYP2C19 may increase the plasma concentration of lansoprazole.

Fluvoxamine: a dose reduction may be considered when combining lansoprazole with the fluvoxamine, an inhibitor of CYP2C19. The plasma concentrations of lansoprazole increase up to 4-fold.

Drugs which induce 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 effects of lansoprazole with NSAIDs have been demonstrated, although no formal interactions studies have been performed.

Therapy of *Helicobacter pylori* infection is intended to be combined with concurrent administration of lansoprazole with two antibiotics. The influence of this combined administration has not yet been investigated systemically. For reasons of theoretical considerations, enhanced interactions with other medicinal products must be expected as a precaution. Monitoring of the serum levels of other medicinal products taken during the first week of eradication therapy is therefore recommended. This concerns particularly such medicinal products also metabolised via the cytochrome P450 system.

The following interactions between lansoprazole and one/two antibiotics used in eradication therapy have been found so far:

| Co-administered medicinal products | Dosage and duration of combined administration | Effect* |
|---|---|---|
| lansoprazole + clarithromycin | 30 mg + 500 mg 3 times/day for 5 days | Increased plasma levels of a clarithromycin metabolite by 16 %; increased bioavailability of lansoprazole by 19 % up to 32 % |
| lansoprazole + amoxicillin | 30 mg + 1000 mg 3 times/day for 5 days | Decelerates uptake of amoxicillin |
| lansoprazole + metronidazole | Not yet investigated | |
| lansoprazole + clarithromycin + amoxicillin | 30 mg + 500 mg + 1000 mg twice daily for 5 days | Increase bioavailability and half-life of lansoprazole by 30 % each; increased plasma levels of a clarithromycin metabolite by 30 % |

## 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.

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 breast-feeding 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. This should be taken into account when driving or using machines.

## 4.8 Undesirable effects

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

The following undesirable effects have been observed during treatment with lansoprazole with the following frequencies:
very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) including isolated reports, not known (cannot be calculated from the available data).

| | **Common (**≥1/100 to <1/10**)** | **Uncommon (**≥1/1,000 to <1/100**)** | **Rare (**≥1/10,000 to <1/1,000**)** | **Very Rare (<1/10,000) Including isolated reports** | **Not known** |
|---|---|---|---|---|---|
| **Gastrointestinal disorders** | Vomiting, nausea, diarrhoea, stomach ache, constipation, flatulence, dry mouth or throat | | Pancreatitis, candidiasis of oesophagus, glossitis, taste disturbances | Colitis, stomatitis | |
| **Skin and subcutaneous tissue disorders** | Rash, urticaria, itching | | Erythema multiforme, petechia, hair loss, photosensitivity purpura | Stevens-Johnson syndrome and toxic epidermal necrolysis | Subacute cutaneous lupus erythematosus |
| **Nervous system disorders** | Headache, dizzines | | Somnolence, vertigo, tremor, paresthesia, restlessness | | |
| **Psychiatric disorders** | | Depression | Insomnia, hallucination, confusion | | |
| **Hepatobiliary disorders** | Increase in liver enzyme levels | | Hepatitis, jaundice | | |
| **Renal and urinary disorders** | | | Interstitial nephritis | | |
| **Blood and lymphatic system disorders** | | Thrombocytopenia, eosinophilia, leucopenia | Anemia. | Agranulocytosis, pancytopenia | |
| **Metabolism and nutritional disorders** | | | | | hypomagnesaemia. (See section 4.4) |
| **Musculoskeletal and connective tissue disorders** | | Fracture of the hip, wrist or spine (see section 4.4) | Arthralgia, myalgia | | |
| **Eye disorders** | | | Visual disturbances | | |
| **Reproductive system and breast disorders** | | | | Gynecomastia | |
| **General disorders and** | Fatigue | Oedema | Angiodema, hyperhidrosis, | Anaphylactic shock | |

| | | | | | |
|---|---|---|---|---|---|
| **administration site conditions** | | | anorexia, impotence, fever | | |
| **Investigations** | | | | Increase in cholesterol and triglyceride levels, hyponatremia | |

Within frequency grouping, undesirable effects are presented in order of decreasing seriousness.

## 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 lansoprazole has been administered up to 180 mg/day orally and up to 90 mg lansoprazole intravenously without significant adverse 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, administration of charcoal and symptomatic therapy are 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 dose of lansoprazole inhibits pentagastrin-stimulated gastric acid secretion by about 80%. After repeated daily administration for seven days, 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 capsule (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.

<u>Absorption</u>
Lansoprazole is rapidly inactivated by gastric acid. Therefore it is formulated as enteric-coated granules in cellulose capsules. Lansoprazole is rapidly absorbed from the duodenum; peak plasma concentrations are achieved within 1.5 – 2.0 hours. Intake of food slows the absorption rate and reduces its bioavailability (AUC) by approximately 50 %.

Distribution
The bioavailability after a single lansoprazole 30 mg dose and after repeated daily administration is 80 – 90%. The bioavailability of lansoprazole may be reduced if antacids and sucralfate are co-administered. Plasma protein binding is approximately 95%. This has no significant effect on other protein bound active substances.

Metabolism
Lansoprazole is mainly metabolised in the liver.
Lansoprazole is mainly catalysed by the enzyme CYP 2C19. CYP 3A4 also contributes to the metabolism of lansoprazole.

Three metabolites have been identified in the plasma: the sulfone, 5-hydroxy lansoprazole and the sulfide. These metabolites have a negligible effect on acid secretion.

Excretion
The elimination half-life of lansoprazole is 1.0 – 2.0 hours. Half life is not changed during repeated dosing of lansoprazole. A single dose of lansoprazole has an inhibitory effect on gastric acid secretion, which lasts for more than 24 hours. Since lansoprazole is activated in the parietal cells, its plasma concentration is not related to gastric acid secretion.

A study with 14C labelled lansoprazole indicated that approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the faeces. Three metabolites have been identified in the urine namely: 5-hydroxy sulfone, 5-hydroxy sulphide and 5-hydroxy lansoprazole.

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..

Pharmacokinetics in renal insufficiency
The bioavailability of lansoprazole is not significantly changed in patients with renal insufficiency.

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/m2 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.

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

**Capsule Content:**
Sugar spheres (sucrose and maize starch)
Sodium starch glycolate Type A
Sodium laurilsulfate
Povidone K30
Potassium oleate
Oleic acid
Hypromellose
Methacrylic acid - ethyl acrylate copolymer 1:1
Triethyl citrate
Titanium dioxide (E171)
Talc

**Capsule Shell:**
Titanium dioxide (E171)
Hypromellose
Carrageenan
Potassium chloride
Carnauba wax
Water

**Printing Ink:**
Shellac
Propylene glycol
Ammonium hydroxide
Potassium hydroxide
Black iron oxide (E172)

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Do not store above 30ºC. Store in the original package.

## 6.5 Nature and contents of container

Al//PA/Al/PVC Blisters within a carton box.

Packs of 7, 14, 28 or 56 capsules (2 x 28 capsules)
Not all pack sizes are marketed.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

## 8 MARKETING AUTHORISATION NUMBER

PA 0749/131/002

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th January 2007

Date of last renewal: 8th December 2010

## 10 DATE OF REVISION OF THE TEXT

March 2013