Public Assessment Report

Decentralised Procedure

Lansoprazole 15 mg Orodispersible Tablets
Lansoprazole 30 mg Orodispersible Tablets

PL 00289/1048-9

UK/H/1144/01/DC

Teva UK Limited
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Teva UK Limited Marketing Authorisations (licences) for the medicinal products Lansoprazole 15 mg and 30 mg Orodispersible Tablets (Product Licence numbers: PL 00289/1048-9). These medicines are available from pharmacies by prescription only.

Lansoprazole is a proton pump inhibitor. Proton pump inhibitors reduce the amount of acid that your stomach makes. Lansoprazole 15 mg and 30 mg Orodispersible Tablets can be used for the following:

- Treatment of duodenal and stomach ulcer
- Treatment of inflammation in your oesophagus (reflux oesophagitis)
- Prevention of reflux oesophagitis
- Treatment of infections caused by the bacteria Helicobacter pylori when given in combination with antibiotic therapy
- Treatment or prevention of duodenal or stomach ulcer in patients requiring continued NSAID treatment (NSAID treatment is used against pain or inflammation)
- Treatment of Zollinger-Ellison syndrome

The data submitted in support of this application for Lansoprazole 15 mg and 30 mg Orodispersible Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

### Information about decentralised procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Lansoprazole 15 mg Orodispersible Tablets Lansoprazole 30 mg Orodispersible Tablets</th>
</tr>
</thead>
</table>
| Type of application (Eudratrack details)         | Level 1  Abridged  
Level 2  Initial  
Level 3  10.1  
Level 4  Chemical substance  
Level 5  Prescription |
| Name of the active substance (INN)                | Lansoprazole |
| Pharmacotherapeutic classification (ATC code)     | Peptic ulcer and gastro-oesophageal disease, proton pump inhibitors (A02BC03) |
| Pharmaceutical form and strength                 | Orodispensible tablet for oral consumption, 15 mg and 30 mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1144/01-02/DC |
| Reference Member State                           | United Kingdom |
| Member States concerned                          | AT, CZ, DE, EL, ES, FR, HU, IE, LU, NL, NO, PL, PT, RO, SE |
| Date of start of the procedure                   | 10 October 2007 |
| End date of decentralised procedure              | 10 September 2009 |
| Marketing Authorisation Number                   | PL 00289/1048-9 |
| Name and address of the authorisation holder      | Teva UK Limited  
Brampton Road  
Hampden Park  
Eastbourne  
BN22 9AG  
East Sussex |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Lansoprazole 15 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 15 mg orodispersible tablet contains 15 mg of lansoprazole.

Excipient(s):
Each 15 mg orodispersible tablet contains 184 mg of lactose, 6.5 mg of aspartame and 31.5 mg of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablet

White to off-white, flat beveled round tablet debossed with "15" on one side of the tablet and plain on the other side.

Each orodispersible tablet contains white to greyish gastroresistant granules.

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 oral 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. It should be taken at least 30 minutes before food (see section 5.2). This medicinal product is strawberry-flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the 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 lansoprazole 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 lansoprazole.

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 lansoprazole 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 aetiological 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).

This medicinal product contains lactose, patients with rare hereditary problems
of galactose intolerance, the Lapp lactase deficiency or glucose-galactose
malabsorption should not take this medicine.

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

This medicinal product contains a source of phenylalanine and may be harmful
for people with phenylketonuria.

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 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/fetal 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 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.

**4.8 Undesirable effects**

Frequencies are defined as 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).

<table>
<thead>
<tr>
<th>Blood and lymphatic system</th>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/1,000, &lt;1/100)</th>
<th>Rare (≥1/10,000, &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombocytopenia,</td>
<td>Anaemia.</td>
<td>Agranulocytosis, pancytopenia.</td>
<td></td>
</tr>
<tr>
<td>Disorders</td>
<td>Eosinophilia, leucopenia.</td>
<td>Psychiatric disorders</td>
<td>Depression. Insomnia, hallucination, confusion.</td>
<td></td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache and dizziness.</td>
<td>Restlessness, vertigo, paresthesia, somnolence, tremor.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>Visual disturbances.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence, dry mouth or throat.</td>
<td>Glossitis, candidiasis of the oesophagus, pancreatitis, taste disturbances.</td>
<td>Colitis, stomatitis.</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Increase in liver enzyme levels.</td>
<td>Hepatitis, jaundice.</td>
<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria, itching, rash.</td>
<td>Petechiae, purpura, hair loss, erythema multiforme, photosensitivity.</td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis.</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, myalgia.</td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Interstitial nephritis.</td>
<td></td>
<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Gynaecomastia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue. Oedema. Fever, hyperhidrosis, angioedema, anorexia, impotence.</td>
<td>Anaphylactic shock.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td>Increase in cholesterol and triglyceride levels, hyponatremia.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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 sulphhydryl 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 orodispersible 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 orodispersible tablets dispersed in a small amount of water and given via syringe directly into the mouth or administered via nasogastric 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 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.

**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

**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 the rete testis.

The clinical relevance of these findings is unknown.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

*Drug Layer:*
Sugar spheres (containing sucrose and maize starch)
Hypermellose
Talc (extra fine)
Magnesium carbonate

*Enteric coat:*
Methacrylic acid-ethyl acrylate copolymer (1:1)
Triethyl citrate

*Compressed tablet:*
Titanium dioxide (E 171)
Colloidal anhydrous silica
Lactose monohydrate
Maize starch
Aspartame
Magnesium stearate
Strawberry flavour

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
18 months

6.4 **Special precautions for storage**
Do not store above 25°C.
Store in the original package to protect from moisture.
6.5 **Nature and contents of container**
PVC/Aluminium/OPA – Aluminium blister packs.

Pack sizes:
1, 7, 14, 28, 30, 30 (3 x 10), 50, 56, 98 & 100 orodispersible tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
East Sussex

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00289/1048

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**
09/10/2009

10 **DATE OF REVISION OF THE TEXT**
09/10/2009
1 NAME OF THE MEDICINAL PRODUCT
Lansoprazole 30 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 30 mg orodispersible tablet contains 30 mg of lansoprazole.

Excipient(s):
Each 30 mg orodispersible tablet contains 367 mg of lactose, 13 mg of aspartame and 63 mg of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablet

White to off white, flat beveled round tablet debossed with "30" on one side of the tablet and plain on the other side.

Each orodispersible tablet contains white to greyish gastroresistant granules.

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 oral 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. It should be taken at least 30 minutes before food (see section 5.2). This medicinal product is strawberry-flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the 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 lansoprazole 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 lansoprazole.
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 lansoprazole 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 aetiological 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).

This medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

This medicinal product contains a source of phenylalanine and may be harmful for people with phenylketonuria.

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 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/fetal 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 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.

4.8 Undesirable effects

Frequencies are defined as 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).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/1,000, &lt;1/100)</th>
<th>Rare (≥1/10,000, &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
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<td>Thrombocytopenia,</td>
<td>Anaemia.</td>
<td>Agranulocytosis,</td>
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<td>eosinophilia, leucopenia.</td>
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<td>pancytopenia.</td>
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<td>Psychiatric disorders</td>
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<td>Depression.</td>
<td>Insomnia, hallucination,</td>
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<td>confusion.</td>
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<td>Nervous system disorders</td>
<td>Headache and dizziness.</td>
<td>Restlessness, vertigo,</td>
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<td></td>
<td></td>
<td>paresthesia, somnolence.</td>
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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 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 orodispersible 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 orodispersible tablets dispersed in a small amount of water and given via syringe directly into the mouth or administered via nasogastric 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 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.

**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.

**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 the rete testis.

The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

*Drug Layer:* Sugar spheres (containing sucrose and maize starch) Hypermellose Talc (extra fine) Magnesium carbonate

*Enteric coat:* Methacrylic acid-ethyl acrylate copolymer (1:1) Triethyl citrate

*Compressed tablet:* Titanium dioxide (E 171) Colloidal anhydrous silica Lactose monohydrate Maize starch Aspartame Magnesium stearate Strawberry flavour

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package to protect from moisture.

6.5 Nature and contents of container
PVC/Aluminium/OPA – Aluminium blister packs.

Pack sizes:
1, 2, 7, 14, 28, 30, 30 (3 x 10), 50, 56, 98 & 100 orodispersible tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements
7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
East Sussex

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/10/2009

10 DATE OF REVISION OF THE TEXT
09/10/2009
LANSOPRAZOLE 15 & 30 MG ORODISPERISABLE TABLETS

PACK LEAFLET INFORMATION

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side-effects gets serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

WHAT LANSOPRAZOLE ORODISPERISABLE TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient in Lansoprazole Orodispersible Tablets is a proton pump inhibitor. Proton pumps inhibit the amount of acid that your stomach makes.

Your doctor may prescribe Lansoprazole Orodispersible Tablets for the following indications:

- Treatment of duodenal and stomach ulcer disease (including infection in your stomach (ulcer) or in your stomach (ulcer))
- Prevention of reflux oesophagitis
- Prevention of heartburn and acid indigestion
- Treatment of infections caused by the bacterium (Helicobacter pylori) when given in combination with antibiotic therapy.
- Treatment or prevention of duodenal or stomach ulcer in patients requiring continued NSAID treatment (NSAID treatment is used against pain or inflammation).
- Treatment of Zollinger-Ellison syndrome.

Your doctor may have prescribed Lansoprazole Orodispersible Tablets for another indication or with a dose different from that which is written in this information leaflet. Please follow your doctor’s instructions for taking your medicine.

BEFORE YOU TAKE LANSOPRAZOLE ORODISPERISABLE TABLETS

Do not take Lansoprazole Orodispersible Tablets:

- If you are allergic (hypersensitive) to Lansoprazole or any of the other ingredients of Lansoprazole Orodispersible Tablets.
- If you are taking a medicine containing an active substance (mocrocrystalline cellulose) used in the treatment of HIV.
- If you are pregnant or breast-feeding.
- If you have any of the following medical conditions:
  - Liver disease
  - Over 65 years of age

Take special care with Lansoprazole Orodispersible Tablets:

Tell your doctor if you have any serious liver disease. The doctor may have to adjust your dosage.

Your doctor may perform or have performed an additional investigation called an endoscopy in order to diagnose your condition.

If diarrhoea occurs during the treatment with Lansoprazole Orodispersible Tablets, contact your doctor immediately, as Lansoprazole Orodispersible Tablets has been associated with a small increase in infectious diarrhoea.

If your doctor has given you Lansoprazole Orodispersible Tablets in addition to other medicines intended for the treatment of Helicobacter pylori infection (antibiotics) or together with anti-inflammatory medicines to treat your pain or inflammatory disease, please also read the package leaflets of these medicines carefully.

If you take Lansoprazole Orodispersible Tablets on a long-term basis (longer than 1 year) your doctor will probably keep you under regular surveillance. You should particularly be aware of any unusual symptoms and circumstances whenever you see your doctor.

Taking other medicines

Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular tell your doctor if you are taking medicines containing any of the following active substances as Lansoprazole Orodispersible Tablets may affect the way they work:

- Itraconazole, ketoconazole, rifampicin (used to treat infections)

Driving and using machines

Side effects such as dizziness, vertigo, tiredness and visual disturbances sometimes occur in patients taking Lansoprazole Orodispersible Tablets. If you experience side effects like these you should take caution as your ability to react may be decreased.

You are responsible to decide if you are in a fit condition to drive a motor vehicle or perform other tasks that demand your full mental and physical abilities.

If you experience side effects that become troublesome, one of the factors that can reduce your ability to do these things safely is your use of medicines.

Description of these effects can be found in other sections.

Read all the information in this leaflet for guidance.

Discuss with your doctor, nurse or pharmacist if you are unsure about anything.

Important information about some of the ingredients of Lansoprazole Orodispersible Tablets:

Lansoprazole Orodispersible Tablets contain lactose and sucrose. If you have been told by your doctor that you have an intolerance to one or more sugars, talk to your doctor before taking this medicine.

Lansoprazole Orodispersible Tablets contain aspartame. Aspartame is a source of phenylalanine, which may be harmful for people with phenylketonuria.

HOW TO TAKE LANSOPRAZOLE ORODISPERISABLE TABLETS

Place the tablets on your tongue and suck gently. The tablet rapidly dissolves in the mouth, releasing microcrystals which you may swallow whole with a glass of water.

Your doctor may instruct you to take the tablet with a swirl in which you have serious difficulties with swallowing.

The following instructions should be followed if administered via syringe:

It is important that the apparatus of the selected syringe is carefully tested.

- Remove the plunger off the syringe (at least 5 ml syringe for the 15 mg tablet and 10 ml syringe for the 30 mg tablet).
- Put the tablet into the syringe.
- Put the plunger back into the syringe.
- For the 15 mg tablet: Draw 4 ml tap water into the syringe.
- For the 30 mg tablet: Draw 10 ml tap water into the syringe.
- Insert the syringes gently for 10-20 seconds until the tablet is dispersed.
- The contents can be emptied directly into the mouth.
- Refill the syringes with 2.5 ml of tap water to flush the remainder out of the syringe into the mouth.

If you are taking Lansoprazole Orodispersible Tablets once a day, try to take it at the same time each day.

If you are taking Lansoprazole Orodispersible Tablets for 8 weeks, this treatment may be followed by a 4 week maintenance dose.

If you are taking Lansoprazole Orodispersible Tablets for more than 8 weeks, this treatment may be followed by a 4 week maintenance dose.

The dose of Lansoprazole Orodispersible Tablets depends on your condition. The usual doses of Lansoprazole Orodispersible Tablets for adults are given below. Your doctor will sometimes prescribe you a different dose and will tell you how long your treatment will last.

Treatment of heartburn and acid reflux: one 15 mg orodispersible tablet every day for 2 weeks.

Treatment of duodenal ulcer: one 30 mg orodispersible tablet every day for 2 weeks.

Treatment of stomach ulcer: one 30 mg orodispersible tablet every day for 4 weeks.

MHRA PAR; LANSOPRAZOLE 15 MG AND 30 MG ORODISPERISABLE TABLETS, PL 00289/1048-9
MHRA PAR; LANSOPRAZOLE 15 MG AND 30 MG ORODISPERSIBLE TABLETS, PL 00289/1048-9

Treatment of inflammation in your oesophagus (reflux oesophagitis): one 30 mg orodispersible tablet every day for 4 weeks.

Long term prevention of reflux oesophagitis: one 15 mg orodispersible tablet every day, your doctor may adjust your dose to one 30 mg orodispersible tablet every day.

Treatment of infection of Helicobacter pylori: The usual dose is one 20 mg orodispersible tablet in combination with two different antibiotics in the morning and one 30 mg orodispersible tablet in combination with two different antibiotics in the evening. Treatment will usually be every day for 7 days.

The recommended combinations of antibiotics are:
- 30 mg Lansoprazole Orodispersible Tablets together with 250-500 mg clarithromycin and 1000 mg amoxicillin
- 30 mg Lansoprazole Orodispersible Tablets together with 250 mg clarithromycin and 400-500 mg metronidazole.

If you are being treated for infection because you have an ulcer, it is unlikely that your ulcer will return if the infection is successfully treated. To give your medicine the best chance of working, take it at the right time and do not miss a dose.

Treatment of duodenal or stomach ulcer in patients requiring continued NSAID treatment: one 30 mg orodispersible tablet every day for 4 weeks.

Prevention of duodenal or stomach ulcer in patients requiring continued NSAID treatment: one 15 mg orodispersible tablet every day, your doctor may adjust your dose to one 30 mg orodispersible tablet every day.

Zollinger-Ellison syndrome: The usual dose is two 30 mg orodispersible tablets every day to start with, then depending on how you respond to Lansoprazole Orodispersible Tablets the dose that your doctor decides is best for you.

Children: Lansoprazole Orodispersible Tablets should not be given to children.

Take your medicine exactly as your doctor has told you. You should check with your doctor if you are not sure how to take your medicine.

If you take more Lansoprazole Orodispersible Tablets than you should:
- If you take more Lansoprazole Orodispersible Tablets than you have been told to, seek medical advice urgently.
- If you forget to take Lansoprazole Orodispersible Tablets:
  - If you forget to take a dose, take it as soon as you remember unless it is nearly time for your next dose. If this happens skip the missed dose and take the remaining orodispersible tablets as normal. Do not take a double dose to make up for a forgotten orodispersible tablet.
  - If you stop taking Lansoprazole Orodispersible Tablets:
  - Do not stop treatment early because your symptoms have got better. Your condition may not have been fully healed and may return if you do not finish your course of treatment.
  - If you have any further questions on the use of this product, ask your doctor.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Lansoprazole Orodispersible Tablets can cause side effects, although not everybody gets them.

The following side effects are common (affects 1 to 10 users in 100):
- 

The following side effects are uncommon (affects 1 to 10 users in 1000):
- 

The following side effects are rare (affects 1 to 10 users in 10,000):
- 

The following side effects are very rare:
- 

In addition to these side effects, you may experience symptoms of angioedema, such as swollen face, tongue or pharynx, difficulty in swallowing, hives and difficulties to breathe.

The following side effects are very rare:

- 

In this leaflet,

If any of the side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5 HOW TO STORE LANSOPRAZOLE ORODISPERSIBLE TABLETS

Keep out of the reach and sight of children.

Do not store above 25°C. Store in the original package to protect from moisture.

Do not use Lanzoprazole Orodispersible Tablets after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What Lansoprazole Orodispersible Tablets contain.

The active substance of Lansoprazole Orodispersible Tablets is Lansoprazole. Each 15 mg orodispersible tablet contains 15 mg of Lansoprazole. Each 30 mg orodispersible tablet contains 30 mg of Lansoprazole.

The other ingredients are sugar syrups (sucrose and maize starch), hypromellose, talc, magnesium carbonate, methocel® K100M

acidic ethanol 45% (1:1) triethyl citrate, titanium dioxide (E 171), colloidal anhydrous silica, lactose monohydrate, maize starch, pregelatinised starch and magnesium stearate.

What Lansoprazole Orodispersible Tablets look like and contents of the pack.

Lansoprazole 15 mg Orodispersible Tablets: White to off-white. Flat bevelled round tablet debelosed with “15” on one side of the tablet and plain on the other side. Each orodispersible tablet contains white to greyish gastroresistant granules.

Lansoprazole 30 mg Orodispersible Tablets: White to off-white. Flat bevelled round tablet debelosed with “30” on one side of the tablet and plain on the other side. Each orodispersible tablet contains white to greyish gastroresistant granules.

Lansoprazole orodispersible tablets are packed in aluminium – aluminium blister packs.

15 mg tablet:
- 1, 2, 3, 4, 8, 10, 20, 30, 40, 50, 60, 80 & 100 orodispersible tablets

30 mg tablet:
- 1, 2, 3, 4, 8, 10, 20, 30, 40, 50, 60, 80 & 100 orodispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturers:

TEVA UK Limited, Eastbourne, BN22 9AG.

This leaflet was last revised in September 2009.
Module 4

Labelling

Foil:
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Lansoprazole 15 mg and 30 mg Orodispersible Tablets in:

- 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.

is approvable.

EXECUTIVE SUMMARY

About the product
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 sulphhydryl group of H+/K+ ATPase causing inhibition of the enzyme activity.

General comments on the submitted dossier
This is a Decentralised Procedure with the United Kingdom acting as the Reference Member State. The application is submitted under Article 10.1 of Directive 2001/83/EC, as amended, cross-referencing to the Lanzor 15mg Magensaftresistente Kapseln (licensed in Germany to Takeda on 4 June 1993). The reference medicinal product in the RMS (UK) is Zoton Fastab 15mg and 30mg (PL 00011/0290 and 0289). Zoton Fastab was licensed to Cyanamid of Great Britain on 24 August 2001 MA holder: John Wyeth & Brother Ltd).

With UK as the Reference Member State in this Decentralized Procedure, Teva UK Limited is applying for Marketing Authorisations for Lansoprazole 15 mg and 30 mg Orodispersible Tablets in AT, CZ, DE, EL, ES, FR, HU, IE, NO, PL, PT, RO, SE and SI.
General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites located outside the Community, the RMS has accepted a copy of the current GMP certificate of satisfactory inspection issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to Lansoprazole 15 mg and 30 mg Orodispersible Tablets are of sufficient quality in view of the present European regulatory requirements. The active substance, lansoprazole is the subject of a Ph Eur monograph. The drug substance specifications are acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An adequate re-test period has been defined based on conducted stability studies.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 18 months with the storage precautions “do not store above 25°C” and “store in the original package to protect from moisture” is acceptable.

NON CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of the drug substance are well known. As lansoprazole is a well known active substance, no further non-clinical data are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a qualified pharmacist who is a Registered Expert in Pharmacology and Toxicology. The overview, dated 20 July 2007, refers to three references from the published literature up to 2007. The
toxicological properties of the drug substances are well known. The nonclinical overview is acceptable.

**CLINICAL ASPECTS**

**Bioequivalence**

Two biostudies demonstrated bioequivalence of the products administered as a 30 mg dose to fasting and fed patients, as follows:

1. **Fasting**
   - Test product: Lansoprazole 30 mg Orodispersible Tablets
   - Reference product: Ogastoro® 30 mg orodispersible tablets (Laboratoires Takeda, France)
   - Dose administered: 30 mg
   - **Results**
     - AUC<sub>t</sub> ratio (90% CI): 100.68% (94.88-106.83)
     - AUC<sub>inf</sub> ratio (90% CI): 100.70% (94.97-106.77)
     - C<sub>max</sub> ratio (90% CI): 92.37% (85.69-99.57)
     - T<sub>max</sub> - test & reference: 2.16 and 1.75 hrs

2. **Fed**
   - Test product: Lansoprazole 30 mg Orodispersible Tablets
   - Reference product: Ogastoro® 30 mg orodispersible tablets (Laboratoires Takeda, France)
   - Dose administered: 30 mg
   - **Results**
     - AUC<sub>t</sub> ratio (90% CI): 99.60% (93.33-106.30)
     - AUC<sub>inf</sub> ratio (90% CI): 99.12% (92.94-105.72)
     - C<sub>max</sub> ratio (90% CI): 101.20% (92.61-110.58)
     - T<sub>max</sub> - test & reference: 4.46 and 4.19 hrs

The 90% confidence intervals for the AUC and C<sub>max</sub> ratios fall within the usual 80-125% bioequivalence range. The test and reference products are, therefore, bioequivalent in the fasting and fed states.

The conclusions of the biostudy carried out with the 30 mg orodispersible tablets can be extrapolated for the other strength. According to the CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the following conditions have to be met for an exemption from bioequivalence studies, when the product differs only in strength of the drug substance:

1. the pharmaceutical products are manufactured by the same manufacturer and process;
2. the drug input has been shown to be linear over the therapeutic dose range (if this is not the case, the strengths where the sensitivity is largest to identify differences in the two products should be used);
3. the qualitative composition of the different strengths is the same;
4. the ratio between amounts of active ingredient and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar;
5. the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.
The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and $C_{\text{max}}$. This is satisfactory.

**Pharmacodynamics**
No new data have been submitted and none are required for this generic application.

**Clinical efficacy**
No new data have been submitted and none are required for this generic application.

**Clinical safety**
No new data have been submitted and none are required for this generic application.

**Pharmacovigilance system**
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Risk Management Plan**
Lansoprazole 15 mg and 30 mg Orodispersible Tablets are generic products. As with the reference medicinal product, no special important risks or potential risks have been identified which require additional risk minimization activities other than the global pharmacovigilance system.

**Product literature**
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**BENEFIT RISK ASSESSMENT**
The object of the present application is to obtain a Marketing Authorisation for a generic formulation of the proton pump inhibitor lansoprazole. This Teva product has been developed in accordance with current regulatory requirements. Bioequivalence of the 30 mg strength with the reference product, Ogastoro® 30 mg orodispersible tablets marketed in France by Takeda, has been demonstrated in two properly conducted studies in the fasting and fed states. The results of the studies conducted with the 30 mg strength can be extrapolated to the 15 mg one.

Lansoprazole is a well-established agent used in the management of gastroduodenal ulceration and acid reflux and hypersecretion disorders. Its efficacy and safety in these indications have been extensively demonstrated in clinical trials and postmarketing use, which also support the recommendations of the proposed Summary of Product Characteristics.

The risk: benefit ratio is, therefore, acceptable.
Module 6

Steps taken after procedure

The following table lists some non-safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/06/2011</td>
<td>Type II variation</td>
<td>To update sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) of the SmPC to remove the details of administration via a nasogastric tube, following new quality data indicating that the use of the product in this manner is not effective in delivering the dose.</td>
<td>Approved 03/12/2011</td>
</tr>
</tbody>
</table>
Annex 1 - Assessment report for variation to update sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) of the SmPC to remove details of administration via a nasogastric tube

**Recommendation**

Based on the review of the data, the RMS considers that variation applications UK/H/1144/001-2/II/013 for Lansoprazole 15 mg and 30 mg Orodispersible Tablets to remove details of administration via a nasogastric tube from sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) of the SmPC are approvable.

**Scientific discussion**

This assessment report concerns Lansoprazole 15 mg and 30 mg Orodispersible Tablets. These were initially licensed in the UK and AT, BE, CZ, DE, DK, EL, ES, FI, FR, HU, IE, LU, NL, PL, PT, RO, SE and SI through a Decentralised Procedure that concluded on 9 October 2009.

The purpose of this variation is to remove reference to the nasogastric tube route of administration from Sections 4.2 and 5.2 of the SmPC.

The justification provided by the applicant for this is as follows:

As the enteric coated pellets are quite large, there is a risk of blockage when passing through the nasogastric tube. Teva has investigated the dispersibility and recovery of Lansoprazole Orodispersible Tablets when administered via a nasogastric tube. It was recognised that recovery is very dependent on the method used (i.e. how much shaking is applied to the syringe, how long it is shaken, etc) and, as such, recovery is not consistently satisfactory.

The instructions in the SmPC concerning administration via a nasogastric tube are currently minimal (“The orodispersible tablets can be dispersed in a small amount of water and administered via a nasogastric tube or oral syringe”). The revised guideline on the Summary of Product Characteristics (Rev. 2, 2009) states that when supportive data are available, information on alternative methods to facilitate administration or acceptability should be given as explicitly as possible, particularly for administration via feeding tubes. Such explicit information is absent from the SmPC and it is not apparent that supportive data are available for this route of administration.

A warning is included on the product labels advising that these products should not be administered via a nasogastric tube.
Following approval of these variations on 3 December 2011 the following updated SmPCs and labels have been incorporated into the Marketing Authorisations:

1 NAME OF THE MEDICINAL PRODUCT
Lansoprazole 15 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 15 mg orodispersible tablet contains 15 mg of lansoprazole.

Excipient(s):
Each 15 mg orodispersible tablet contains 184 mg of lactose, 6.5 mg of aspartame and 31.5 mg of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablet

White to off-white, flat beveled round tablet debossed with "15" on one side of the tablet and plain on the other side.

Each orodispersible tablet contains white to greyish gastroresistant granules.

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 oral 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. It should be taken at least 30 minutes before food (see section 5.2). This medicinal product is strawberry-
flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the 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 oral syringe.

Administration via nasogastric tube is not recommended.

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 lansoprazole 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 lansoprazole.

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 lansoprazole 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 aetiological 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).

This medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

This medicinal product contains a source of phenylalanine and may be harmful for people with phenylketonuria.

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/fetal development, parturition or postnatal development.

Therefore, the use of lansoprazole during pregnancy is not recommended.

**Breastfeeding:**

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.

**4.8 Undesirable effects**

Frequencies are defined as 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).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/1,000, &lt;1/100)</th>
<th>Rare (≥1/10,000, &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia,</td>
<td></td>
<td>Anaemia,</td>
<td>Agranulocytosis,</td>
<td></td>
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<tr>
<td>System</td>
<td>Common Adverse Reactions</td>
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<tr>
<td><strong>Immune system disorders</strong></td>
<td>eosinophilia, leucopenia.</td>
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<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Angioedema Anaphylactic shock.</td>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Depression. Inomnia, hallucination, confusion.</td>
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<td></td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Headache and dizziness. Restlessness, vertigo, paresthesia, somnolence, tremor, taste disturbances.</td>
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<tr>
<td><strong>Eye disorders</strong></td>
<td>Visual disturbances.</td>
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<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence, dry mouth or throat.</td>
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<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Increase in liver enzyme levels.</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Urticaria, itching, rash.</td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Arthralgia, myalgia.</td>
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<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Interstitial nephritis.</td>
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<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td>Gynaecomastia, impotence.</td>
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<td><strong>General disorders and administration site conditions</strong></td>
<td>Fatigue. Oedema.</td>
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<tr>
<td><strong>Investigations</strong></td>
<td>Increase in investigations.</td>
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</table>
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 sulphhydryl 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 orodispersible 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 orodispersible tablets dispersed in a small amount of water and given via syringe directly into the mouth 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 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.

**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.

**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 the rete testis.

The clinical relevance of these findings is unknown.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Drug Layer:**

Sugar spheres (containing sucrose and maize starch)
Hypromellose
Talc (extra fine)
Magnesium carbonate

**Enteric coat:**

Methacrylic acid-ethyl acrylate copolymer (1:1)
Triethyl citrate

**Compressed tablet:**

Titanium dioxide (E 171)
Colloidal anhydrous silica
Lactose monohydrate
Maize starch
Aspartame
Magnesium stearate
Strawberry flavour
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
18 months

6.4 **Special precautions for storage**
Do not store above 25°C.
Store in the original package to protect from moisture.

6.5 **Nature and contents of container**
PVC/Aluminium/OPA – Aluminium blister packs.

Pack sizes:
1, 7, 14, 28, 30, 30 (3 x 10), 50, 56, 98 & 100 orodispersible tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
East Sussex

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00289/1048

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/10/2009

10 **DATE OF REVISION OF THE TEXT**
03/12/2011
1 NAME OF THE MEDICINAL PRODUCT
Lansoprazole 30 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 30 mg orodispersible tablet contains 30 mg of lansoprazole.

Excipient(s):
Each 30 mg orodispersible tablet contains 367 mg of lactose, 13 mg of aspartame and 63 mg of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablet

White to off white, flat beveled round tablet debossed with "30" on one side of the tablet and plain on the other side.

Each orodispersible tablet contains white to greyish gastroresistant granules.

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 oral 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. It should be taken at least 30 minutes before food (see section 5.2). This medicinal product is strawberry-flavoured and should be placed on the tongue and gently sucked. The tablet rapidly disperses in the mouth, releasing the 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 oral syringe.

Administration via nasogastric tube is not recommended.

**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 lansoprazole 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 lansoprazole.

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 $\geq 65$ 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 lansoprazole 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 aetiological 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).

This medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

This medicinal product contains a source of phenylalanine and may be harmful for people with phenylketonuria.

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/fetal development, parturition or postnatal development.

Therefore, the use of lansoprazole during pregnancy is not recommended.

Breastfeeding:
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.

4.8 Undesirable effects
Frequencies are defined as 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).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/1,000, &lt;1/100)</th>
<th>Rare (≥1/10,000, &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia, eosinophilia, leucopenia.</td>
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<td></td>
<td>Anemia.</td>
<td>Agranulocytosis, pancytopenia.</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Angioedema</td>
<td>Anaphylactic shock</td>
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<tr>
<td>Metabolism and</td>
<td></td>
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<td>Anorexia</td>
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<tr>
<td>nutrition disorders</td>
<td>Psychiatric disorders</td>
<td>Nervous system disorders</td>
<td>Gastrointestinal disorders</td>
<td>Eye disorders</td>
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<tr>
<td>Depression.</td>
<td>Insomnia, hallucination, confusion.</td>
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<td></td>
<td>Restlessness, vertigo, paresthesia, somnolence, tremor, taste disturbances.</td>
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<tr>
<td>Eye disorders</td>
<td>Visual disturbances.</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence, dry mouth or throat.</td>
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<td></td>
<td>Glossitis, candidiasis of the oesophagus, pancreatitis, taste disturbances.</td>
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<td></td>
<td>Colitis, stomatitis.</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>Increase in liver enzyme levels.</td>
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<td></td>
<td>Hepatitis, jaundice.</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria, itching, rash.</td>
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<td></td>
<td>Petechiae, purpura, hair loss, erythema multiforme, photosensitivity, hyperhidrosis.</td>
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<td></td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis.</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, myalgia.</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Interstitial nephritis.</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Gynaecomastia, impotence.</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue.</td>
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<td></td>
<td>Oedema.</td>
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<td></td>
<td>Fever.</td>
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<tr>
<td>Investigations</td>
<td>Increase in cholesterol and triglyceride levels, hyponatremia.</td>
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</tbody>
</table>
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 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 orodispersible 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 orodispersible tablets dispersed in a small amount of water and given via syringe directly into the mouth 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 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.

**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.

**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 the rete testis.

The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Drug Layer:
Sugar spheres (containing sucrose and maize starch)
Hypromellose
Talc (extra fine)
Magnesium carbonate

Enteric coat:
Methacrylic acid-ethyl acrylate copolymer (1:1)
Triethyl citrate

Compressed tablet:
Titanium dioxide (E 171)
Colloidal anhydrous silica
Lactose monohydrate
Maize starch
Aspartame
Magnesium stearate
Strawberry flavour

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package to protect from moisture.

6.5 **Nature and contents of container**
PVC/Aluminium/OPA – Aluminium blister packs.

Pack sizes:
1, 2, 7, 14, 28, 30, 30 (3 x 10), 50, 56, 98 & 100 orodispersible tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
East Sussex

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00289/1049

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/10/2009

10 **DATE OF REVISION OF THE TEXT**
03/12/2011
Lansoprazole 15 mg Orodispersible Tablets:

Each orodispersible tablet contains 15 mg of lansoprazole. Also contains lactose, sorbitol and aspartame. See enclosed leaflet for further information.

DOSEAGE:
- Oral use. The tablets can be sucked or swallowed whole with a glass of water.
- Do not crush or chew.
- Please read the enclosed package leaflet before use. Use as directed by the doctor.
- Do not administer by nasogastric tube.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
- Do not store above 25°C. Store in the original package to protect from moisture.
Lansoprazole 30 mg Orodispensible Tablets:

Each orodispersible tablet contains 30 mg of lansoprazole. Also contains lactose, sucrose and aspartame. See enclosed leaflet for further information.

USAGE: Oral use. The tablets can be sucked or swallowed whole with a glass of water. Do not crush or chew. Please read the enclosed package leaflet before use. Use as directed by the doctor. Do not administer by nasogastric tube.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not store above 25°C. Store in the original package to protect from moisture.