

## **ANNEX I**

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL  
PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT, MARKETING  
AUTHORISATION HOLDERS IN THE MEMBER STATES**

<b><u>Member State</u></b>	<b><u>Marketing Authorisation Holder</u></b>	<b><u>Applicant</u></b>	<b><u>Invented name</u></b>	<b><u>Strength</u></b>	<b><u>Pharmaceutical Form</u></b>	<b><u>Route of administration</u></b>
Austria	-	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	Lansohexal 15 mg - Hartkapseln	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansohexal 30 mg - Hartkapseln	30 mg	Gastro-resistant capsule, hard	Oral use
Denmark	-	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	Lansoprazol HEXAL	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansoprazol HEXAL	30 mg	Gastro-resistant capsule, hard	Oral use
Germany	-	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	Lansohexal 15 mg Hartkapseln	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansohexal 30 mg Hartkapseln	30 mg	Gastro-resistant capsule, hard	Oral use
Finland	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	-	Lansoprazol HEXAL 15mg	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansoprazol HEXAL 30 mg	30 mg	Gastro-resistant capsule, hard	Oral use
Sweden	-	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	Lansocid	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansocid	30 mg	Gastro-resistant capsule, hard	Oral use

## **ANNEX II**

### **SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA**

## SCIENTIFIC CONCLUSIONS

### OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LANSOPRAZOL HEXAL 15 MG, 30 MG GASTRO-RESISTANT CAPSULES, HARD (see Annex I)

Lansoprazol HEXAL 15 mg, 30 mg, gastro-resistant capsules, hard were referred for arbitration according to Article 29 of Council Directive 2001/83/EC, as amended, following concerns raised by Germany during a Mutual Recognition Procedure with Finland acting as Reference Member state. The SPC of the reference product in Germany does not contain the indications related to the concomitant use of NSAIDs and the treatment and prevention of gastric and duodenal ulceration caused by these compounds.

- Treatment of benign gastric and duodenal ulcers associated with the use of anti-inflammatory analgesics in patients requiring continued anti-inflammatory analgesic treatment.

Gastric acid is central in the pathogenesis of gastroduodenal ulcers and acid inhibition has been shown to effectively heal NSAID induced ulcers. In patients who continue to take NSAID medication healing is delayed.

**Agrawal et al** conducted a double-blind RCT in 353 patients with gastric ulcer and who continued to receive stable doses of NSAIDs. Patients were randomized to treatment with either ranitidine 150 mg twice daily or lansoprazole, 15 mg or 30 mg once daily for 8 weeks. Healing was assessed endoscopically at 4 and 8 weeks. After 8 weeks of treatment, healing was observed in 61 (53%) of 115, 81 (69%) of 118, and 85 (73%) of 117 patients receiving ranitidine, lansoprazole 15 mg, and lansoprazole 30 mg, respectively ( $P < 0.05$  for ranitidine vs. both lansoprazole doses). At 4 weeks, the corresponding healing rates were 30%, 47% and 57%. For duodenal ulcers ( $n=46$ ), the healing rates were between 81%-93% at week 8 in the 3 treatment groups. Safety was comparable between the groups. **Matsukawa et al** evaluated in an uncontrolled study the efficacy of lansoprazole 15 mg and 30 mg in 47 patients with NSAID induced gastroduodenal ulcers. Patients with duodenal ulcers ( $n=3$ ) were treated for 6 weeks and patients with gastric ulcers ( $n=42$ ) or multiple ulcers ( $n=5$ ) for 8 weeks. Overall rate of healing according to Sakitas classification was 95%. The rate of S2-healing (good healing) was 35%. **Campbell et al** evaluated the effect of pre-treatment of *Helicobacter pylori* (*H. pylori*) infection on gastric ulcer healing rates in patients receiving NSAIDs and antisecretory medication in pooled analyses of two identical double-blind RCT comparing lansoprazole with ranitidine. In total 692 patients were enrolled. Simple healing rates (independent of *H. pylori* status) were at 8 weeks, 66%, 74% and 50% in the lansoprazole 15 mg, 30 mg and ranitidine groups, respectively; ( $P < 0.001$ ). In patients receiving NSAIDs with *H. pylori* infection gastric ulcer healing with an antisecretory agent was significantly enhanced (70% vs 61%,  $P < 0.05$ ). In a study published as an abstract (**Goldstein et al**), the healing rates were 64% and 76% for the 15 mg and 30 mg dose, respectively, at week 8. At week 4 the healing rates were 44% and 51% for the 15 mg and 30 mg dose, respectively.

The proton pump inhibitors, omeprazole, lansoprazole and pantoprazole are all mainly metabolized by the cytochrome P450 isoform CYP2C19. All three have a very limited potential for drug interactions at the CYP level (**Unge and Andersson 1997**). Interaction with NSAIDs has not been suggested.

- Prophylaxis of gastric and duodenal ulcer associated with the use of anti-inflammatory agents and relief of symptoms in patients requiring continuous anti-inflammatory therapy

Three published papers on the clinical evidence for prevention of NSAID related ulcers are submitted. **Lai et al** studied 123 patients with ulcer complications relating to the use of low dose aspirin and who were infected by *H. pylori*. After successful healing of the ulcers and eradication of *H. pylori*, patients were randomized to treatment with lansoprazole 30 mg or placebo in addition to aspirin 100 mg daily for 12 months. Primary endpoint was the recurrence of ulcer complications. During follow-up, 9/61 patient (14.8%) in the placebo group had recurrence of ulcer complications compared with 1/62 patients (1.6%) in the lansoprazole group ( $P=0.008$ ). **Graham et al** conducted a prospective; double blind RCT

among 537 patients without *H. pylori* infection who were long-term users of NSAIDs with a history of endoscopically documented gastric ulcer. Patients were randomized to receive placebo, misoprostol or lansoprazole 15 mg or 30 mg for 12 weeks. Ulcer status was determined by endoscopy at week 4, 8, and 12. By week 12, the percentages of gastric ulcer-free patients were 51%, 93%, 80% and 82% for the placebo, misoprostol, lansoprazole 15 mg and lansoprazole 30 mg group, respectively. Antacid use was significantly less among patients in the lansoprazole groups compared with patients in the misoprostol and placebo groups. Patients in the lansoprazole groups had significantly less abdominal pain compared with patients in the misoprostol group. **Lai et al** studied 43 patients who presented with peptic ulcer and were found to be infected with *H. pylori* while receiving NSAIDs. Patients received eradication treatment followed by lansoprazole 30 mg for 4 weeks. Patients with healed ulcers and *H. pylori* eradicated then received naproxen 750 mg daily and were randomized to receive either lansoprazole 30 mg or no treatment for 8 weeks. The primary endpoint was recurrence of symptomatic and complicated ulcers during the 8 weeks. Endoscopy was also performed at week 8. The cumulative incidence of symptomatic and complicated GD ulcers at week 8 was 4.5% in the lansoprazole group and 42.9% in the no treatment group ( $P=0.0025$ ).

### **Benefit/Risk considerations**

The bibliographic data submitted by the applicant show that in patients who continue to receive NSAID medication, lansoprazole is more effective in healing gastric ulcers than  $H_2$ -receptor antagonist and the healing rates are acceptable although somewhat lower than reported for omeprazole. There is scarce data concerning healing rates for duodenal ulcers but duodenal ulcers are known in general to heal better than gastric ulcers following acid suppression. The limited data as regards lansoprazole support this. No formal interaction studies with lansoprazole and NSAIDs have been performed. Several clinical trials as well as extensive clinical experience has not indicated that there exist interactions when lansoprazole is given together with NSAIDs. Furthermore, interaction studies performed with omeprazole and several NSAIDs have not shown any interaction. The lack of formal interaction studies with NSAIDs has to be adequately reflected in the SPC.

The bibliographic data submitted provide evidence to support the indications:

- Treatment of NSAID-associated benign gastric and duodenal ulcers in patients requiring continuous NSAID-treatment”
- Prophylaxis of NSAID-associated benign gastric and duodenal ulcers patients at risk requiring continuous NSAID-treatment”.

An indication that includes relief of symptoms in this population, however, is not sufficiently supported. Compared with placebo, lansoprazole only reduced the need for antacids in one of the studies but significant difference with regard to symptoms was not shown.

Therefore, the benefit-risk profile of Lansoprazol HEXAL 15 mg, 30 mg in the proposed indications can be considered favourable.

### **GROUND FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS**

Whereas,

- The scope of the referral was to agree on a Summary of Products Characteristics in view of the indication.
- The Summary of Products Characteristic proposed by the applicant has been assessed based on the documentation submitted and the scientific discussion within the Committee.

the CHMP has recommended the granting of the Marketing Authorisations with amendments of the Summary of Product Characteristics as set out in Annex III for Lansoprazol HEXAL and associated names (see Annex I).

**ANNEX III**

**AMENDED SUMMARY OF PRODUCT CHARACTERISTICS  
OF THE REFERENCE MEMBER STATE**

**Note: This SPC is the one that was Annexed to the Commission Decision on this Article 29 referral for lansoprazole containing medicinal products. The text was valid at that time.**

**After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.**

## **1. NAME OF THE MEDICINAL PRODUCT**

Lansoprazole and associated names (see Annex I), 15 mg gastro-resistant capsule, hard  
Lansoprazole and associated names (see Annex I), 30 mg gastro-resistant capsule, hard

[See Annex I - to be completed nationally]

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 15 or 30 mg lansoprazole.

[To be completed nationally]

For excipients, see 6.1.

## **3. PHARMACEUTICAL FORM**

Gastro-resistant capsule, hard

15 mg:

Opaque, yellow hard gelatine capsule, containing pellets with enteric coating.

30 mg:

Opaque, white hard gelatine capsule, containing pellets with enteric coating.

[To be completed nationally]

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic Indications**

- Treatment of duodenal and gastric ulcer confirmed by endoscopy or radiography.
- Treatment of reflux oesophagitis.
- Long-term prophylaxis of reflux oesophagitis.
- Zollinger-Ellison syndrome.
- Treatment of NSAID-associated benign gastric and duodenal ulcers in patients requiring continuous NSAID-treatment
- Prophylaxis of NSAID-associated gastric and duodenal ulcer in patients at risk requiring continuous NSAID-treatment

### **4.2. Posology and Method of Administration**

#### 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 should be 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 should be continued at the same dose for another 4 weeks.

Treatment of reflux oesophagitis:

The recommended dose of lansoprazole 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.

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.

Benign NSAID-associated gastric and duodenal ulcers:

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 be considered.

Prophylaxis of NSAID-associated gastric and duodenal ulcers in patients requiring continuous 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 once daily. Relief of symptoms is obtained rapidly. Individual adjustment of dosage should be considered. If the symptoms are not relieved within 4 weeks with a daily dose of 30 mg, further examinations are recommended.

Impaired hepatic or renal function:

There is no need to change the dose in patients with impaired renal function. The normal daily dose of 30 mg should not be exceeded in these patients, however. Care should be exercised in the administration of lansoprazole in patients with mildly to moderately impaired hepatic function. In mildly impaired patients, the dose should not exceed 30 mg. In patients with moderately impaired hepatic function, the dose should be restricted to 15 mg daily. Due to the lack of data in patients with severely impaired hepatic function, these patients should not be treated with lansoprazole (see section 4.4 “Special warning and precautions for use”).

Children:

Lansoprazole is not recommended in children as safety and efficacy have not been established in this population.

Elderly: Due to delayed elimination of lansoprazole in the elderly it may be necessary to administer the treatment in doses of 15-30 mg adjusted to individual requirements. However, the daily dose in the elderly should not exceed 30 mg.

The capsules are swallowed whole with liquid. The capsules may be emptied, but the contents may not be chewed or ground. Concomitantly taken food slows down and reduces the absorption of lansoprazole. This medicine has the best effect when taken into empty stomach.

#### **4.3. Contraindications**

Hypersensitivity to lansoprazole or any of the excipients of the product.

#### **4.4. Special Warning and Precautions for Use**

The diagnosis of gastroduodenal ulcers and reflux oesophagitis should be confirmed by endoscopy or other appropriate diagnostic means. Reflux oesophagitis may not present as ulceration and/or visual damage, therefore in certain cases endoscopy alone may not be sufficient.



The possibility of malignant gastric tumour should be excluded before initiating treatment of gastric ulcer with lansoprazole, because lansoprazole can mask the symptoms and delay the diagnosis.

Lansoprazole should be used with caution in patients with severe hepatic dysfunction. (See Section 4.2 “Posology and method of administration”)

Lansoprazole has a similar mechanism of action to omeprazole and both increase gastric pH, the following statement is made by analogy to omeprazole. Decreased gastric acidity due to lansoprazole increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with lansoprazole may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Patients suffering from gastro-duodenal ulcers, the possibility of *H. pylori* infection as an etiological factor should be considered.

If lansoprazole, in combination with antibiotics, is used for eradication therapy of *H.-pylori*, then also instructions for the use of these antibiotics should 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 benefit risk assessment should regularly be performed in these patients (see “5.3 Preclinical safety data”).

If visual disturbances occur during long-term use (>1 year), an ophthalmologist should be consulted.

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

#### **4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**

##### *Drugs associated with cytochrome P450*

As lansoprazole is metabolised via a drug metabolising enzyme system associated with cytochrome P450 (CYP2C19 and CYP3A4), interactions with drugs metabolised via the same enzyme system are possible.

The effects of other drugs on lansoprazole

##### *Drugs which inhibits CYP2C19*

Drugs which inhibit CYP2C19 may increase the plasma concentration of lansoprazole. Fluvoxamine, an inhibitor of CYP2C19, increased the plasma concentrations of lansoprazole up to 4-fold.

##### *Drugs which inhibits CYP3A4*

Drugs which inhibit CYP3A4 such as ketokonazole, itraconazole, protease inhibitors, macrolides etc may markedly increase the plasma concentrations of lansoprazole.

Effects of lansoprazole on other drugs

##### *Ketoconazole and itraconazole*

The absorption of ketoconazole and itraconazole from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of lansoprazole may result in subtherapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided. The effect may also be present if lansoprazole is combined with other drugs with pH dependent absorption.

### *Digoxin*

Coadministration of lansoprazole and digoxin may lead to increased digoxin plasma levels. In patients receiving digoxin, the plasma levels should therefore be monitored and the dose of digoxin adjusted if necessary.

### Drugs metabolised by CYP3A4

Lansoprazole may give rise to increased plasma concentrations of drugs metabolised by CYP3A4. Caution is advised when combining lansoprazole with drugs which are metabolised by this enzyme.

### *Tacrolimus*

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

### *Carbamazepine*

Caution is advised during cotreatment with carbamazepin (a CYP3A substrate) and lansoprazole. The drug combination may result in increased carbamazepin concentrations as well as reduced lansoprazole concentrations.

### *Phenytoin*

Studies have shown that the dosage of phenytoin (CYP2C19 and CYP2C9 substrate) may have to be reduced when administered concomitantly with lansoprazole. Caution and monitoring of phenytoin plasma concentrations is advised when initiating and ending lansoprazole treatment.

### *Warfarin*

Caution and increased monitoring frequency is advised when initiating or ending lansoprazole co-treatment in patients treated with warfarin.

### *Theophyllin*

Lansoprazole gives a 14% reduction in the plasma concentrations of theophyllin. Individual patients may receive a clinically relevant decrease. Caution is advised when combining the two drugs.

Clinically significant interactions of lansoprazole with nonsteroidal anti-inflammatory drugs or diazepam have not been demonstrated. Formal interaction studies with lansoprazole and NSAIDs have not been conducted.

Antacids and sucralfate may decrease the bioavailability of lansoprazole. The lansoprazole dose should therefore be taken at least an hour prior or after.

Lansoprazole has been observed to inhibit the transport protein, P-glycoprotein (Pgp) in vitro. It may not be excluded that lansoprazole may affect transport via this protein giving rise to increased plasma concentrations of P-gp substrates such as digoxin.

*Caution should be exercised when combining lansoprazole with drugs which have a narrow therapeutic index, as the effect of lansoprazole on the metabolism of other drugs has not been extensively investigated.*

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

<b>Co-administered medicinal products</b>	<b>Dosage and duration of combined administration</b>	<b><u>Effect*</u></b>
<b>lansoprazole + clarithromycin</b>	30 mg + 500 mg 3 times/day for 5 days	Increased plasma levels of a clarithromycin metabolite by 16 %; increased bioavailability of lansoprazole by 19 % up to 32 %

<b>lansoprazole + amoxicillin</b>	30 mg + 1000 mg 3 times/day for 5 days	Decelerates uptake of amoxicillin
<b>lansoprazole + metronidazole</b>	Not yet investigated	
<b>lansoprazole + clarithromycin + amoxicillin</b>	30 mg + 500 mg + 1000 mg twice daily for 5 days	Increase bioavailability and half-life of lansoprazole by 30 % each; increased plasma levels of a clarithromycin metabolite by 30 %

\*The effects of clarithromycin on the pharmacokinetics of lansoprazole are likely to be dependent on the patient's CYP2C19 genotype. A poor metaboliser would have more marked effects than an extensive metaboliser.

The intake of food reduces the bioavailability of lansoprazole: it is recommended to take lansoprazole before the meal.

#### 4.6. Pregnancy and Lactation

For lansoprazole no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

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

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 and fatigue may occur (see section 4.8 undesirable effects). Under these conditions the ability to react may be decreased. This should be taken into account when driving or using machines. (see section 4.8 Undesirable effects).

#### 4.8. Undesirable Effects

	<b>Common (&gt;1%)</b>	<b>Uncommon (0.1-1%)</b>	<b>Rare (0.01-0.1%)</b>	<b>Very Rare (&lt;0.01%)</b>
<b>Gastrointestinal</b>	nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence and dyspepsia.		dry mouth or throat, glossitis, Candidiasis of oesophagus, pancreatitis	colitis, stomatitis and black tongue
<b>Skin and hair</b>	eczema, urticaria and itching.		petechia, purpura, hair loss, erythema multiforme, stevens-Johnson syndrome and toxic epidermal necrolysis.	
<b>Nervous system</b>	headache, dizziness		restlessness, insomnia, drowsiness, depression,	

			hallucination, confusion, vertigo and paresthesia, somnolence, tremor.	
<b>Liver and kidneys</b>		Increase in liver enzyme levels.	hepatitis, icterus and interstitial nephritis.	
<b>Blood</b>			thrombocytopenia, eosinophilia, pancytopenia and agranulocytosis, anemia, leucopenia.	agranulocytosis
<b>Cardiovascular</b>			peripheral edema, palpitation and chest pain.	
<b>Musculoskeletal and connective tissue disorders</b>			muscle and joint pain	
<b>Senses</b>			taste disturbances and visual disturbances.	
<b>Endocrine disorders</b>				gynecomastia, galactorrhoea.
<b>General</b>	fatigue.		fever, hyperhidrosis, bronchial constriction, impotence and angioedema.	anaphylactic shock, general malaise
<b>Investigations</b>				Increase in cholesterol and triglyceride levels.

#### 4.8. Overdose

The effects of overdose of lansoprazole in humans are not known (although the acute toxicity is likely to be low) and, consequently, instructions for treatment cannot be given. However, daily doses of up to 180 mg of lansoprazole have been administered in trials without significant undesirable effects.

Please refer to section 4.8. Undesirable effects for possible symptoms of lansoprazole overdose.

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 30 mg 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 30 mg daily, and most patients with duodenal ulcer recover within 2 weeks, patients with gastric ulcer and reflux oesophagitis within 4 weeks.

### **5.2. Pharmacokinetic Properties**

#### Absorption and distribution:

Lansoprazole is rapidly inactivated by gastric acid and lansoprazole is consequently administered as enteric coated granules in gelatin capsules. Absorption from the duodenum is rapid and plasma peak concentration is achieved within 1.5-2.0 hours. Bioavailability after a single dose of 30 mg and after repeated daily administration is 80-90%. Intake of food slows the absorption rate of lansoprazole and reduces its bioavailability (AUC) by about 25%. Antacids and sucralfate may reduce the bioavailability of lansoprazole. The plasma protein binding of lansoprazole is about 95%, but this has not been found to have a significant effect on other protein bound drugs.

#### Metabolism and elimination:

The metabolism of lansoprazole is mainly catalysed by the enzyme CYP2C19. The enzyme CYP3A4 also contributes to the metabolism. 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).

The elimination half-life of lansoprazole is 1.0-2.0 hours. There is no change in half-life during treatment. A single dose of lansoprazole has an inhibitory effect on gastric acid secretion lasting more than 24 hours. Since lansoprazole is activated in the parietal cells, its plasma concentration is not related to gastric acid inhibition. Lansoprazole is mainly metabolised in the liver. Three metabolites have been identified in the plasma: the sulphone, 5-hydroxy lansoprazole and the sulphide. These metabolites have no significant effect on acid secretion. About 15-50% of the metabolites are secreted in the urine and the remainder in the faeces. Three metabolites have been identified in the urine: 5-hydroxy sulphone, 5-hydroxy sulphide and 5-hydroxy lansoprazole. In patients with cirrhosis the AUC of lansoprazole is significantly increased and the elimination half-life is prolonged, but no signs of accumulation of lansoprazole have been detected. The bioavailability of lansoprazole is not significantly changed in renal insufficiency. Elimination of lansoprazole in the elderly is slightly delayed.

### **5.3. Preclinical Safety Data**

Preclinical data reveal no special hazard 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 and retinal atrophy. Retinal atrophy occurred not until 18 months of treatment. This was not seen in monkeys, dogs or mice. In mice dose-related gastric ECL cell hyperplasia developed as well as liver tumours and adenoma of rete testis. The clinical relevance of these findings is unknown.

Results of studies on carcinogenic potential show that lansoprazole therapy is associated with Leydig cell hyperplasia and benign Leydig cell tumours in rats.

Intestinal metaplasia has been found in animal studies on rats. The clinical relevance of these findings is unknown.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of Excipients**

Sugar spheres (sucrose and maize starch)  
Sodium laurilsulphate  
Meglumine  
Mannitol  
Hypromellose  
Macrogol 6000  
Talc  
Polysorbate 80  
Titanium dioxide (E 171)  
methacrylic acid ethyl acrylate copolymer, 1:1, dispersion 30 %

#### Capsule shell:

Gelatin  
Titanium dioxide (E 171)

In addition for Lansoprazole 15 mg:  
Quinoline yellow (E 104)

[To be completed nationally]

### **6.2. Incompatibilities**

Not applicable

### **6.3. Shelf life**

3 years

### **6.4. Special Precautions for Storage**

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

### **6.5. Nature and Contents of Container**

Aluminium/Aluminium blister (Alu/OPA/PVC/PE)

#### *Lansoprazole 15 mg:*

7, 10, 14, 15, 20, 28, 30, 35, 50, 56, 60, 84, 98, 100 and 250 capsules

#### *Lansoprazole 30 mg:*

2, 7, 10, 14, 15, 20, 28, 30, 35, 42, 50, 56, 60, 98, 100 and 250 capsules

Not all pack sizes may be marketed.

[To be completed nationally]

### **6.6. Instructions for Use and Handling**

No special requirements.

[To be completed nationally]

**7. MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**8. MARKETING AUTHORISATION NUMBER**

[To be completed nationally]

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION**

[To be completed nationally]

**10. DATE OF REVISION OF THE TEXT**