ANNEX I

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

Member State	Marketing Authorisation Holder	Applicant	Invented name	Strength	Pharmaceutical Form	Route of administration
Belgium	-	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	Lansoprazole BEXAL 15 mg gélules gastro-resistantes	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansoprazole BEXAL 30 mg gélules gastro-resistantes	30 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	Lansoprazol HEXAL 15 mg Hartkapseln	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansoprazol HEXAL 30 mg Hartkapseln	30 mg	Gastro-resistant capsule, hard	Oral use
Finland	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	-	Lansopon 15mg	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansopon 30 mg	30 mg	Gastro-resistant capsule, hard	Oral use
Luxembourg	-	HEXAL AG Industriestraße 25 D-83607 Holzkirchen	Lansoprazol HEXAL 15 mg Hartkapseln	15 mg	Gastro-resistant capsule, hard	Oral use
			Lansoprazol HEXAL 30 mg Hartkapseln	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 LANSOPON 15 MG, 30 MG, GASTRO-RESISTANT CAPSULES, HARD (see Annex I)

Lansopon 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 concerns rose referred to discrepancies in comparison to the reference products on posology.

Eradication of H. pyolori and peptic ulcer healing

Eradication of *H. pylori* has been shown to be a definitive cure for duodenum ulcer and most gastric ulcers. It has also been proven that eradication prevents ulcer recurrence without any maintenance antisecretory therapy.

Lansoprazole 30 mg combined with amoxicillin 1g, clarithromycin 250 or 500 mg, or metronidazole 400 mg twice daily was associated with eradication rates ranging from 71 to 94%, and ulcer healing rates were generally >80% in well designed studies. Preliminary data suggest that lansoprazole-based eradication therapy is effective in children and the elderly. Triple therapies with a proton pump inhibitor, clarithromycin and either amoxycillin or metronidazole are the most widely accepted treatment for *Helicobacter pylori* infection. Combinations of lansoprazole with one or two antibiotics produced equivalent eradication of *H. pylori*. Fourteen-day, proton pump inhibitor-based triple therapy achieves better results than 7-day schedules.

A meta-analysis of studies comparing twice daily, one-week triple therapy with a proton pump inhibitor, clarithromycin (C) and amoxycillin (A) (PCA) vs. those using proton pump inhibitor, clarithromycin and a nitroimidazole (N) (PCN) for *H. pylori* eradication provided evidence in support of similar *H. pylori* eradication efficacy.

The combination of lansoprazole with antibiotics either as double or triple therapy has demonstrated an *H. pylori* eradication rate of between 80 and 90%. Triple therapy allows the eradication of *H. pylori* in more than 85% of cases in patients with peptic ulcer.

Benefit/Risk considerations

Available data support the use of lansoprazole-amoxicillin-clarithromycin as a first-line treatment. In case of clarithromycin resistance, or treatment failure, the combination of lansoprazole-amoxicillin-metronidazole may be used, and in case of beta-lactam allergy the combination of lansoprazole-clarithromycin-metronidazole is advisable. However, in order to avoid treatment failure, local antibacterial resistance patterns and local guidelines should be considered.

The risk/benefit ratio of Lansopon 15 mg, 30 mg is considered to be favourable provided that appropriate information regarding *H. pylori* eradication therapy are included in the SPC.

GROUNDS 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 posology for eradication therapy for *H. pylori*
- 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 Lansopon 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

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

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.

Eradication of *Helicobacter pylori*:

30 mg lansoprazole 2 times daily for one week in combination with one of the following three combinations:
a) amoxicillin 1 g twice daily + clarithromycin 500 mg twice daily,
b) clarithromycin 250 mg twice daily + metronidazole 400-500 mg twice daily,
c) amoxicillin 1 g twice daily + metronidazole 400-500 mg twice daily.

Consideration should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents.

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 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 warnings 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.

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 ketoconazol and itraconazol and the combination should be avoided. The effect may also be present if lansoprazole is combined with other drugs with pH dependent absorption.

Digoxin
Coadminitration 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.

<u>Drugs metabolised by CYP3A4</u>
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 lanzoprazole is initiated or ended.

Carbamazepine
Caution is adviced 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
Lansoprazol 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, though formal interaction studies with lansoprazole and NSAIDs have not been conducted.

Antacids and sucralfate may decrease the bioavailabilty 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 lanzoprazole 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.

Therapy of Helicobacter pyloti infection is intended to be combined with concurrent administration of lansoprazole, clarithromycin and a further antibiotic. The influence of this combined administration has not yet been investigated systemically. For reasons of theoretical considerations, enhanced interactions with other medicinal products must be expected as a precaution. Monitoring of the serum levels of other medicinal products taken during the 1-week eradication therapy is therefore recommended. This concerns particularly such medicinal products also metabolized via the cytochrome P450 system.

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

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

amoxicillin		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.

4.6. 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

	Common (>1%)	**Uncommon (0.1-1%)**	**Rare (0.01-0.1%)**	**Very Rare (<0.01%)**
Gastrointestinal	nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence and dyspepsia.		dry mouth or throat, glossitis, candidiasis of oesophagus, pancreatitis	colitis, stomatitis and black tongue.
Skin and hair	eczema, urticaria and itching.		petechia, purpura, hair loss, erythema multiforme, stevens-Johnson syndrome and toxic epidermal necrolysis.	
Nervous system	headache, dizziness		restlessness, insomnia, drowsiness, depression, hallucination, confusion, vertigo and paresthesia, somnolence, tremor.	
Liver and kidneys		Increase in liver enzyme levels.	hepatitis, icterus and interstitial nephritis.	

Blood			thrombocytopenia, eosinophilia, pancytopenia and agranulocytosis, anemia, leucopenia.	agranulocytosis
Cardiovascular			peripheral edema, palpitation and chest pain.	
Musculoskeletal and connective tissue disorders			muscle and joint pain	
Senses			zaste disturbances and visual disturbances.	
Endocrine disorders				gynecomastia, galactorrhoea.
General	fatigue.		fever, hyperhidrosis, bronchial constriction, impotence and angioedema.	anaphylactic shock, general malaise
Investigations				Increase in cholesterol and triglyceride levels.

4.9. 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 CYUP3A4 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 25ºC.
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.

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