IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0126/181/001
Case No: 2053305

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Losamel 10mg gastro-resistant capsules, hard

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **03/04/2009** until **02/04/2014**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Losamel 10mg gastro-resistant capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Losamel 10mg capsules: one capsule contains 10mg of omeprazole.

- Each 10mg capsule contains 51 to 58mg of sucrose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsules, hard
Opaque yellow capsule containing off-white to cream-white spherical microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Duodenal ulcers
- Benign gastric ulcers
- Reflux oesophagitis
- Maintenance treatment of reflux oesophagitis to prevent relapse
- Symptomatic treatment of gastro-oesophageal reflux disease
- Zollinger-Ellison syndrome
- Treatment of NSAID (Non Steroidal Anti Inflammatory Drug) related gastric and duodenal ulcers
- Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with *Heliobacter pylori* associated peptic ulcers (see section 4.2)
- Children over 1 year of age and ≥ 10 kg: Reflux oesophagitis. Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease.

4.2 Posology and method of administration

Duodenal ulcers
The usual dose is 20 mg once daily. The duration of the treatment is 2-4 weeks.

Maintenance treatment:
In maintenance treatment for prevention of recurrence of duodenal ulcers not responding to eradication of *Helicobacter pylori* the treatment should be individualised depending on the clinical response. The normal dose is 20mg daily. For some patients 10mg may be sufficient.

Benign gastric ulcers:
The usual dose is 20 mg once daily. The duration of the treatment is 4-(6)-8 weeks.

Reflux oesophagitis:
The usual dose is 20 mg once daily. The duration of treatment is 4-8 weeks.

Notes:
In isolated cases of duodenal ulcers, benign gastric ulcers and reflux oesophagitis the dosage of omeprazole can be increased to 40 mg omeprazole once daily.

Only if eradication therapy is not indicated or has been unsuccessful, duodenal and gastric ulcers may be treated with omeprazole monotherapy.

Children over 1 year of age and ≥ 10 kg.
Reflux oesophagitis:
The treatment time is 4-8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastrooesophageal reflux disease
The treatment time is 2-4 weeks If symptom control has not been achieved after 2-4 weeks the patient should be investigated further.

The dosage recommendations are as follows:

Age	**Weight**	**Dosage**
≥ 1 year of age	10-20 kg	10 mg once daily.
The dosage can be increased to 20 mg once daily if needed.		
≥ 2 years of age	> 20 kg	20 mg once daily.
The dosage can be increased to 40 mg once daily if needed.		

Maintenance treatment of reflux oesophagitis to prevent relapse:
The usual dose is 10 to 20 mg depending on the clinical response.

Zollinger-Ellison syndrome:
The dosage should be adjusted individually and continued under specialist supervision as long as clinically indicated. The recommended initial dosage is 60 mg once daily. With doses above 80 mg daily, the dose should be divided and given twice daily. In patients with Zollinger-Ellison syndrome the treatment is not subject to a time limit.

Treatment of NSAID related gastric and duodenal ulcers:
The usual dose is 20 mg daily. The treatment duration is 4 to 8 weeks.

Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse:
The usual dose is 20 mg daily.

Symptomatic treatment of gastro-oesophageal reflux disease:
The usual dose is 10 to 20 mg daily depending on clinical response. The treatment duration is 2 to 4 weeks. If the patient does not experience any improvement in symptoms after a 2 week treatment further examinations should be performed.

Eradication therapy:
Patients with peptic ulcers due to *Helicobacter pylori* infection should be treated with eradication therapy with appropriate combinations of antibiotics with adequate dosing regimens. The selection of an appropriate regimen should be based on patient tolerability and therapeutic guidelines. The following combinations have been tested:

- Omeprazole 20 mg, Amoxicillin 1000 mg, Clarithromycin 500 mg all 2 times daily
- Omeprazole 20 mg, Clarithromycin 250 mg, Metronidazole 400-500 mg all 2 times daily

The treatment duration for the eradication is 1 week. To avoid the development of resistance the treatment duration should not be reduced.
In patients with active ulcers an extension of the therapy with omeprazole-monotherapy according to the posology and treatment duration given above may be performed.

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. Metronidazole should not be considered as first choice because of mutagenic and carcinogenic properties in animal studies.

Children over 4 years of age
In combination with antibiotics in treatment of duodenal ulcer caused by 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 treatment should be supervised by a specialist.

Weight	**Dosage**
15-≤30 kg	Combination with two antibiotics: Omeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together 2 times daily for 1 week.
30-≤40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered 2 times daily for 1 week.
>40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 1 g and Clarithromycin 500 mg are all administered 2 times daily for 1 week.

Special populations

Elderly
Dose adjustment is not required in the elderly.

Children
Omeprazole is not intended for children under 1 year of age.

Impaired renal function:
Dose adjustment is not required in patients with impaired renal function.

Impaired hepatic function:
The dose should be reduced in patients with impaired hepatic function. The maximum daily dose is 20 mg (see also 4.4).

Method of administration:
The capsules should be swallowed whole with sufficient fluid (e.g. 1 glass of water) before a meal (e.g. breakfast or dinner) on an empty stomach. The capsules should not be chewed or crushed.

For use in treating patients with swallowing difficulties or young children the capsules may be opened and the contents suspended in a small amount of fruit juice or yoghurt after gentle mixing. Resulting dispersions should be taken immediately.

4.3 Contraindications

Omeprazole is contraindicated in patients with hypersensitivity to omeprazole or to any of the excipients.
Combination therapy with clarithromycin should not be used in patients with hepatic impairment.
Omeprazole is contraindicated in patients taking atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

In patients with peptic ulcer disease *Helicobacter pylori*-status should be determined if relevant. In patients who are shown to be *Helicobacter pylori*-positive, the elimination of the bacteria by eradication therapy should be aimed wherever possible.
If a gastric ulcer is suspected, the possibility of malignancy must be excluded before treatment with Losamel capsules is instituted, as treatment may alleviate symptoms and delay diagnosis

The diagnosis of reflux oesophagitis should be confirmed endoscopically.

Decreased gastric acidity, due to any means – including proton-pump inhibitors – increases gastric counts of bacteria normally present in the gastro-intestinal tract. Treatment with acid-reducing medicinal products leads to a slightly increased risk of gastrointestinal infections, such as Salmonella and Campylobacter.

In patients with severe impaired hepatic function, liver enzyme values should be checked periodically during treatment with Losamel capsules (see also 4.2).

To ensure better efficacy in treatment of NSAID-related ulcers, the possibility of stopping the intake of the causative agent should be strongly considered.

The maintenance treatment of ulcers associated with the intake of NSAIDs should be restricted to patients at risk.

Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment and thorough risk-benefit assessment should be performed in long-term use exceeding 1 year.

During therapy with omeprazole requiring a combined administration of medicinal products (NSAID related ulcers or eradication) caution should be exercised when administering additional medicinal products as interactions might add up or potentiate (see section 4.5)

During combination treatment caution should also be exercised in patients with renal or hepatic dysfunction (for dose restriction see section 4.2).
Omeprazole should not be used in infants and children under the age of 1 year.
Some children with chronic illnesses may require long-term treatment although it is not recommended.

Although not known for orally administered omeprazole, blindness and deafness have been reported in the use of the injection form of omeprazole; therefore, in severely ill patients the monitoring of visual and auditory senses is recommended.

Warnings relating to excipients present in the product:

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed with adults.

Effects of omeprazole on the pharmacokinetics of other drugs

Drugs with pH dependent absorption

Atazanavir
Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, Cmax and Cmin).

Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. Thus, PPIs including omeprazole should not be co-administered with atazanavir.

Although not studied, other daily doses of omeprazole may produce similar results and, therefore, also co-administration of any other doses of omeprazole is contraindicated (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 omeprazole may result in sub therapeutic concentrations of ketoconazole and itraconozole and the combination should be avoided.

Digoxin
Simultaneous treatment with omeprazole and digoxin in healthy subjects lead to a 10 % increase in the bioavailability of digoxin.

Drugs metabolised by CYP2C19 and CYP2C9 (including warfarin, phenytoin and voriconazole)
As omeprazole is metabolised in the liver by the cytochrome P450 enzyme system, it can inhibit the isoenzymes CYP 2C19 and CYP2C9 which can cause increased plasma concentrations of other drugs metabolised by these enzymes. This has been observed for diazepam (and also for other benzodiazepines such as triazolam or flurazepam), phenytoin and warfarin. Periodic monitoring of patients receiving warfarin or phenytoin is recommended when starting and discontinuing omeprazole treatment and an adjustment of warfarin or phenytoin dose may be necessary. Other drugs that could be affected are hexabarbital, citalopram, imipramine, clomipramine etc.
Omeprazole (40 mg daily) increased Cmax and AUC_{τ} for voriconazole (CYP219 substrate) 15% and 41%, respectively. Voriconazole increased omeprazole AUC_{τ} by 280%. When used together, dose adjustment for omeprazole should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Disulfiram
Omeprazole may inhibit the hepatic metabolism of disulfiram. Some possibly related cases of muscular rigidity have been reported.

Ciclosporin
There are contradictionary data on the interaction of omeprazole with ciclosporin. Therefore,the plasma levels of ciclosporin should be monitored in those patients treated with omeprazole, because an increase in ciclosporin levels is possible.

Tacrolimus
Although conflicting data have been reported, concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus. Therefore this combination should be used cautiously.

Clarithromycin
Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration.

Vitamin B12
Omeprazole may reduce the oral absorption of vitamin B12. This should be taken into account in those patients with low basal levels who undergo a long-term treatment with omeprazole.

St. John’s wort
Because of a potentially clinically significant interaction St. John’s wort should not be used concomitantly with omeprazole.

Other medicines and alcohol
There is no evidence of an interaction of omeprazole with caffeine, propranolol, theophylline, metoprolol, lidocaine, quinidine, phenacetin, oestradiol, amoxycilln, budesonide, diclofenac, metronidazole, naproxen, piroxicam, or antacids. The absorption of omeprazole is not affected by alcohol.

4.6 Pregnancy and lactation

Limited epidemiologic studies indicate no adverse effects on pregnancy or increases in general malformation rate. However, there is insufficient information with respect to specific abnormalities.

In rats, omeprazole and its metabolites are excreted into milk. There is insufficient data on exposure of babies via breast milk. Omeprazole concentration in human breast milk reaches ca 6% of the maximum plasma concentration in the mother. Use of omeprazole during pregnancy and lactation requires a careful benefit-risk assessment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines with concomitant intake of omeprazole have been performed. However, adverse reactions such as drowsiness, somnolence and visual disturbances may occur (See section 4.8). Under these conditions the ability to drive and use machines may be impaired.

4.8 Undesirable effects

The following definitions apply to the incidence of the undesirable effects:
- very common (1/10)
- common (1/100 to <1/10)
- uncommon (1/1,000 to <1/100)
- rare (1/10,000 to <1/1,000)
- very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders	Rare: Hypochrome, microcytic anaemia in children. Very rare: changes in blood count, reversible thrombocytopenia, leucopenia or pancytopenia and agranulocytosis.
Nervous system disorders	Common: somnolence, sleep disturbances (insomnia), dizziness, headaches and drowsiness. These complaints usually improve during continued therapy. Rare: Paresthesia and light headedness. Mental confusion and hallucinations in predominantly severely ill or elderly patients. Very rare: agitation and depressive reactions in predominantly severely ill or elderly patients.
Eye disorders	Uncommon: visual disturbances (blurred vision, loss of visual acuity or reduced field of vision). These conditions usually resolve on cessation of therapy.
Ear and labyrinth disorders	Uncommon: auditory dysfunction (e.g. tinnitus). These conditions usually resolve on cessation of therapy.

Gastrointestinal disorders	Common: diarrhoea, constipation, flatulence (possibly with abdominal pain), nausea and vomiting. In the majority of these cases the symptoms improve if the therapy is continued. Uncommon: taste disturbances. This condition usually resolves on cessation of therapy. Rare: brownish-black discoloration of the tongue during concomitant administration of clarithromycin and benign glandular cysts: both were reversible after cessation of treatment. Very rare: dryness of the mouth, stomatitis, candidiasis or pancreatitis.
Renal and urinary disorders	Very rare: nephritis (interstitial nephritis)
Skin and subcutaneous tissue disorders:	Uncommon: pruritus, skin eruptions, alopecia, erythema multiforme or photosensitivity and increased tendency to sweat. Very rare: Stevens-Johnson-syndrome or toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Rare: muscle weakness, myalgia and joint pain.
General disorders and administration site conditions	Uncommon: peripheral oedema (which resolved on cessation of therapy) Very rare: hyponatremia.
Immune system disorders	Very rare: urticaria, elevated body temperature, angioedema, bronchoconstriction, or anaphylactic shock, allergic vasculitis and fever.
Hepatobiliary disorders	Uncommon: changes in liver enzyme values (which resolve after discontinuation of therapy). Very rare: hepatitis with or without jaundice, hepatic failure and encephalopathy in patients with pre-existing severe liver disease.
Reproductive system and breast disorders	Very rare: Gynaecomastia

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 yrs with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long term data regarding the effects of omeprazole treatment on puberty and growth.

4.9 Overdose

There is no information available on the effects of overdosage of omeprazole in humans. Large single oral doses up to 160 mg/day and daily doses up to 400 mg as well as intravenous single doses up to 80 mg and daily intravenous doses up to 200 mg or 520 mg in 3 days, respectively, have been tolerated without undesirable effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02B C 01

Omeprazole, a substituted benzimidazole, is a gastric proton pump inhibitor, i.e. omeprazole directly and dose-dependently inhibits the enzyme H^+,K^+-ATPase, which is responsible for the gastric acid secretion in the gastric parietal cells. Due to this selective intracellular mode of action and the low affinity for other membrane-bound receptors (such as the histamine H_2, muscarine M_1 or gastrinergic receptors), omeprazole has been assigned to a separate class of acid-inhibiting agents, which block the final step of acid production.

As a consequence of its mode of action, omeprazole leads to an inhibition of both basal and stimulable acid secretion, irrespective of the stimulus type. Thus, omeprazole increases the pH-value and reduces the volume of gastric acid secretion.

As a weak base the prodrug omeprazole accumulates in the acid environment of the parietal cells and will only become effective as an inhibitor of the H^+, K^+-ATPase after being protonised and rearranged.

In an acid environment at a pH of less than 4 the protonised omeprazole is converted to omeprazole sulphenamide, the active substance proper. Compared to the plasma half-life of the omeprazole base, omeprazole sulphenamide remains in the cell for a longer period of time (see section 5.2). A sufficiently low pH-value is only found in the gastric parietal cells; this explains the high specificity of omeprazole. It is the omeprazole sulphenamide that binds to the enzyme and inhibits its activity.

If the enzyme-system is inhibited, the pH-value increases and less omeprazole accumulates or is converted in the gastric parietal cells. Consequently, the accumulation of omeprazole is regulated by a kind of feedback-mechanism.

In long-term treatment, omeprazole, as a result of acid inhibition, causes a moderate gastrin increase. Mild to moderate increase in ECL-cells occurs during long-term use. Carcinoids as found in animal experiments (see section 5.3) were not seen in humans yet.

Most available clinical experience from controlled randomised clinical trials indicate that omeprazole 20 mg twice daily in combination with two antibiotics for 1 week achieve >80% *Helicobacter pylori* eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant *Helicobacter pylori* isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for *Helicobacter pylori* eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antibacterial agent should be taken into account in the considerations for a new retreatment regimen.

Clinical evidence additionally indicates that, following successful eradication therapy in patients with peptic ulcer disease, relapse rates of duodenal ulcers and most likely also gastric ulcers are exceptionally low in comparison to the natural course of the disease with ongoing infection.

Paediatric data:
In a non-controlled study in children (1 to 16 yrs of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0-24 months with clinically diagnosed GERD were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50 % after 8 weeks of treatment irrespective of the dose.

Eradication of Helicobacter pylori in children:
A randomised, double blind clinical study (Héliot study) has concluded to the efficacy and an acceptable safety for omeprazole associated to two antibiotics (amoxicilline and clarithromycine) in the treatment of Helicobacter pylori infection in children of 4 years old and above with a gastritis: Helicobacter pylori eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicilline + clarithromycine versus 9.4% (3/32 patients) with amoxicilline + clarithromycine. However, there was no evidence of clinical benefit demonstrated regarding dyspeptic symptoms. This study does not support any information for children aged less than 4 years old.

5.2 Pharmacokinetic properties

Absorption
Omeprazole is acid labile and is administered orally as gastro-resistant granules in hard-gelatin capsules. Absorption takes place in the small intestine. Peak plasma concentrations of omeprazole occur within 1 to 3 hours after administration. The bioavailability of a single oral dose of omeprazole is approximately 35%. With repeated administration the bioavailability increases to approximately 60%.

Distribution
The distribution volume of omeprazole in the body is relatively small (0.3 L/kg of body weight) and corresponds to that of the extracellular fluid. Approximately 95 % is protein bound.

Elimination
Omeprazole is entirely metabolised, mainly in the liver by CYP 2C19.
After intravenous administration of 40 mg omeprazole for 5 days, the absolute measured bioavailability increased by about 50 %; this can be explained by decreased hepatic clearance due to saturation of the CYP2C19 enzyme. The sulphone, sulphide and hydroxy-omeprazole are found in plasma. These metabolites have no significant effect on acid secretion. About 20 % of administered dose is excreted in faeces and the remaining 80 % is excreted in urine as metabolites. The two major urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid. The plasma half-life is about 40 minutes, and the total plasma clearance is 0.3 to 0.6 L/min.

Relationship between plasma concentration and effect
Omeprazole accumulates as a weak base in the acid environment of the intracellular channel system of the parietal cells. In this acid environment omeprazole is protonised and converted into the active substance, omeprazole sulphenamide. The active substance binds covalently to the gastric proton pump (H^+,K^+-ATPase) on the secretory surface of the gastric parietal cell and inhibits its activity. The duration of the inhibition of acid secretion is therefore substantially longer than the period in which omeprazole-base is present in plasma. The degree of inhibition of acid secretion is directly correlated to the area under the plasma concentration-time curve (AUC) but not to the plasma concentration at any given time.

Special populations

Elderly
The bioavailability of omeprazole is slightly elevated in the elderly, and the elimination rate is slightly diminished. But the individual values are nearly equal to that of young healthy subjects, and there is no indication that the tolerance in elderly patients treated with normal doses of omeprazole is reduced.

Children
During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

Impaired renal function
In patients with renal impairment the kinetics of omeprazole was very similar to that in healthy subjects. But, because the renal elimination is the most important excretory pathway for metabolised omeprazole, the elimination rate is reduced to a degree corresponding to the reduction in renal function. If omeprazole is given once daily, accumulation can be avoided.

Impaired hepatic function
In patients with chronic hepatic disease the clearance of omeprazole is reduced, and the plasma half-life can increase up to approximately 3 hours. The bioavailability can then be greater than 90 %. Omeprazole given in a dosage regime of 20 mg once daily for 4 weeks was tolerated well, and no accumulation of omeprazole or its metabolites was observed.

CYP2C19 poor metabolisers
In a small percentage of the patients (CYP 2 C19 poor metabolisers)with genes coding for a non-functional CYP2C19 enzyme, a reduced elimination of omeprazole has been observed. In these cases, the terminal elimination half-life can be approximately 3 times as long as the normal value, and the area under the plasma concentration-time curve (AUC) can increase by up to 10 times.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

Gastric ECL-cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole or subjected to partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules content:
Sugar spheres (consisting of corn starch and sucrose)
Sodium laurilsulfate
Anhydrous disodium phosphate
Mannitol (E421)
Hypromellose
Macrogol 6000
Talc
Polysorbate 80
Titanium dioxide (E171)
Methacrylic Acid-Ethyl Acrylate Copolymer

Capsule shell:
Gelatin
Quinoline yellow aluminium lake (E104)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store below 25°C
OPA/Al/PVC-Al blister: Store in the original package to protect from moisture.
HDPE bottle: Keep the bottle tightly closed to protect from moisture.

6.5 Nature and contents of container

OPA/Al/PVC-Al blister:
7, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100, 140, 280 and 500 capsules
HDPE bottle with silica gel desiccant contained in the polypropylene lid:
5, 7, 14, 15, 28, 30, 50, 56, 60, 90 and 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
Co Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/181/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd April 2009

10 DATE OF REVISION OF THE TEXT