Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Omeprazole Mylan 10 mg Gastro-resistant capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mg Gastro-resistant capsule, hard contains 10 mg omeprazole

Excipients with known effect
Each 10 mg Gastro-resistant capsule, hard contains 16.9 mg sucrose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsules, hard
Capsule with light pink opaque cap and white opaque body, hard shell gelatine capsule filled with white to off-white pellets. The capsule is axially printed with 'MYLAN' over 'OM10' in black ink on cap and body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Omeprazole is indicated in adults and children over 1 year of age and ≥ 10kg.

Omeprazole gastro-resistant capsules are indicated in:

Adults

- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcer
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcer
- In combination with appropriate antibiotics, *Helicobacter pylori* (*H. pylori)* eradication in peptic ulcer disease
- Treatment of NSAID associated gastric and duodenal ulcers
- Prevention of NSAID associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux esophagitis
- Long term management of patients with healed reflux esophagitis
- Treatment of symptomatic gastro-esophageal reflux disease,
- Treatment of Zollinger-Ellison syndrome

Paedriatric population
Children over 1 year of age and ≥10 kg

- Treatment of reflux esophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

Children and adolescents over 4 years of age

- In combination with antibiotics in the treatment of duodenal ulcer caused by *H. pylori*

4.2 Posology and method of administration

Posology in adults

Treatment of duodenal ulcers

The recommended dose in patients with an active duodenal ulcer is Omeprazole 20 mg once daily. In most patients healing occurs within two weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further two weeks treatment period. In patients with a poorly responsive duodenal ulcer Omeprazole 40mg once daily is recommended and healing is usually achieved within four weeks.

Prevention of relapse of duodenal ulcers

For the prevention of relapse of duodenal ulcer in *H. pylori* negative patients or when *H. pylori* eradication is not possible the recommended dose is Omeprazole 20mg once daily. In some patients a daily dose of 10 mg may be sufficient. In case of therapy failure, the dose can be increased to 40mg.

Treatment of gastric ulcers

The recommended dose is 20mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period. In patients with poorly responsive gastric ulcer Omeprazole 40mg once daily is recommended and healing is usually achieved within eight weeks.

Prevention of relapse of gastric ulcers

For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is Omeprazole 20mg once daily. If needed the dose can be increased to omeprazole 40mg once daily.

H. pylori eradication in peptic ulcer disease

For the eradication of *H. pylori* the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.

- Omeprazole 20 mg + clarithromycin 500 mg + amoxicillin 1000 mg, each twice daily for 1 week or
- Omeprazole 20 mg + clarithromycin 250 mg (alternatively 500 mg) + metronidazole 400mg-(or 500 mg or tinidazole 500mg) each twice daily for one week or
- Omeprazole 40 mg once daily with amoxicillin 500 mg + metronidazole 400mg (or 500 mg or tinidazole 500mg) both three times a day for one week

In each regimen, if the patient is still *H. pylori* positive, therapy may be repeated.

Treatment of NSAID - associated gastric and duodenal ulcers:

For the treatment of NSAID -associated gastric and duodenal ulcers, the recommended dose is Omeprazole 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period.

Prevention of *NSAID -associated gastric and duodenal ulcers in patients at risk*

For the prevention of NSAID -associated gastric ulcers and duodenal ulcers in patients at risk (age >60, previous history of gastric and duodenal ulcers, previous history of upper GI bleeding) the recommended dose is omeprazole 20mg once daily.

Treatment of reflux esophagitis

The recommended dose is Omeprazole 20mg once daily. In most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period.

In patients with severe esophagitis Omeprazole 40mg once daily is recommended and healing is usually achieved within eight weeks.

Long-term management of patients with healed reflux esophagitis

For the long-term management of patients with healed reflux esophagitis the recommended dose is omeprazole 10 mg once daily. If needed, the dose can be increased to Omeprazole 20-40mg once daily.

Treatment of symptomatic gastro-esophageal reflux disease
The recommended dose is Omeprazole 20mg daily. Patients may respond adequately to 10mg daily, and therefore individual dose adjustments should be considered. If symptom control has not been achieved after four weeks treatment with Omeprazole 20mg daily, further investigation is recommended.

Treatment of Zollinger-Ellison syndrome
In patients with Zollinger-Ellison syndrome the dose should be individually adjusted and treatment continued as long as clinically indicated. The recommended initial dose is Omeprazole 60 mg daily. All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of Omeprazole 20-120 mg daily. When the dose exceeds Omeprazole 80 mg daily, the dose should be divided and given twice daily.

Paediatric population

The safety and efficacy of Omeprazole in children aged 0-12 months and < 10kg has not yet been established.

Children over 1 year of age and ≥ 10 kg
Treatment of Reflux esophagitis

Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

The posology recommendations are as follows:

Age	Weight	Posology
≥ 1 year of age	10 – 20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed
≥ 2 year of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed

Reflux esophagitis: The treatment time is 4-8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal 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.

Children and adolescents over 4 years of age
Treatment of duodenal ulcer caused by H pylori.
When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidelines 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.

The posology recommendations are as follows:

Weight	Posology
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
31-40 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:
Renal impairment
Dose adjustment is not required in patients with impaired renal function (see section 5.2).

Hepatic impairment
In patients with impaired hepatic function a daily dose of 10-20 mg may be sufficient (see section 5.2).

Elderly
Dose adjustment is not required in the elderly (see section 5.2).

Method of administration:
It is recommended to take Omeprazole capsules in the morning, preferably without food, swallowed whole with half a glass of water.
The capsules must not be crushed or chewed.
For patients with swallowing difficulties and for children who can drink or swallow semi-solid food:
Patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid e.g. fruit juice or apple sauce, or in non-carbonated water. Patients should be advised that the dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water.

Alternatively patients can suck the capsule and swallow the pellets with half a glass of water. The enteric-coated pellets must not be chewed.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients listed in section 6.1.
Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20mg should not be exceeded.

Omeprazole, as with all acid blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolized through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPIs like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or other medicines that may cause

hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fractures by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference omeprazole treatment should be stopped for at least five days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

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

Each 40mg Gastro-resistant capsule, hard contains Sunset Yellow (E110) and Allura red (E129). These may cause allergic reactions.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and in hospitalised patients possibly also *Clostridium difficile* (see section 5.1).

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Paediatric population:
Some children with chronic illnesses may require long-term treatment although it is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of omeprazole on the pharmacokinetics of other active substances

Active substances with pH dependent absorption
The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir
The plasmas levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3) Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75-90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ ritonavir 100 mg to healthy volunteers resulted in a 75% decrease in atazanavir exposure. Increasing the atazanavir dose to 400mg did not compensate for the effect of omeprazole on atazanavir exposure. The co-administration of omeprazole (20mg once daily) with atazanavir

400 mg/ritonavir 100mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300mg/ ritonavir 100 mg once daily.

Digoxin
Concomitant treatment with omeprazole (20mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged (see section 4.4).

Other active substances
The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19
Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol
Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased the C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Phenytoin
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

<u>Unknown Mechanism</u>

Saquinavir
Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus
Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Methotrexate
When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4
Since Omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 and

CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's Wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy
Results from three prospective epidemiologic studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/ newborn child.
Omeprazole can be used during pregnancy.

Breast-feeding
Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

4.7 Effects on ability to drive and use machines

Omeprazole has no or negligible influence on the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbance may occur (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related.
Adverse reactions listed below are classified according to the frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention:
- 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)

SOC/ Frequency	**Adverse reaction**
Blood and lymphatic system disorders	
Rare:	Leukopenia, thrombocytopenia
Very rare:	Pancytopenia, agranulocytosis
Immune system disorders	
Rare:	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/ shock
Metabolism and nutrition disorders	
Rare:	Hyponatraemia
Not Known:	Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	

Uncommon:	Insomnia
Rare:	Agitation, confusion, depression
Very Rare:	Aggression, hallucinations.
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, somnolence
Rare:	Taste disturbance
Eye disorders	
Rare:	Blurred vision
Ear and labyrinth disorders	
Uncommon:	Vertigo
Respiratory, thoracic and mediastinal disorders	
Rare:	Bronchospasm
Gastrointestinal disorders	
Common:	Abdominal pain, constipation, diarrhoea, flatulence, nausea and vomiting, fundic gland polyps (benign)
Rare:	Dry mouth, stomatitis, gastrointestinal candidiasis
Not known:	Microscopic colitis
Hepatobiliary disorders	
Uncommon:	Increased liver enzymes
Rare:	Hepatitis with or without jaundice
Very Rare:	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	
Uncommon:	Dermatitis, pruritus, rash, urticaria
Rare:	Alopecia, photosensitivity
Very Rare:	Erythema multiforme, Stevens-Johnsons syndrome, toxic epidermal necrolysis (TEN)
Not known	Subacute cutaneous lupus erythematosus (see section 4.4)S
Musculoskeletal and connective tissue disorders	
Uncommon:	Fracture of the hip, wrist or spine (see section 4.4)
Rare:	Arthralgia, myalgia
Very Rare:	Muscular weakness
Renal and urinary disorders:	
Rare:	Interstitial nephritis
Reproductive System and breast disorders:	
Very Rare:	Gynaecomastia
General disorders and administration site conditions	
Uncommon:	Malaise, peripheral oedema
Rare:	Increased sweating.

Paediatric Population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2. Tel: +353 1 6764971, Fax: +353 1 6762517. Website: www.hpra.ie, E-mail: medsafety@hpra.ie

4.9 Overdose

There is limited information available on the effects of overdoses of omeprazole in humans. In literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have been reached of up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described in connection with omeprazole overdose have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC-code: A02BC01

Mechanism of Action:

Omeprazole, a racemic mixture of two enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H^+, K^+-ATPase – the acid pump. This effect on the final step of gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

Pharmacodynamic effects:
All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Clinical Efficacy and Safety:

Effect on gastric acid secretion:
Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained on duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the esophagus in patients with gastro-esophageal reflux disease. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not the actual plasma concentration at a given time.

No tachyphylaxis has been observed during treatment with omeprazole.

Effect on H. pylori

H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* is a major factor in the development of atrophic gastritis which is associated with an increased

risk of developing gastric cancer.

Eradication of *H. pylori* with omeprazole and antimicrobials is associated with high rates of healing and long-term remission of peptic ulcers.

Dual therapies have been tested and have been found to be less effective than triple therapies. They could however be considered in cases where known hypersensitivity precludes the use of any triple combination.

Other effects related to acid inhibition

During long-term treatment gastric glandular cysts have been reported in somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly also *Clostridium difficile*.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

Paediatric population
In a non-controlled study in children (1 to 16 years of age) with severe reflux esophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved esophagitis level in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0-24 months with clinically diagnosed gastro-oesophageal reflux disease 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 (Heliot study) concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin) was safe and effective in the treatment of *H. pylori* infection in children of 4 years old and above with a gastritis: *H. pylori* eradication rate: 74 % (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4 % (3/32 patients) with amoxicillin + clarithromycin. 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 therefore administered orally as enteric-coated granules in hard-gelatin capsules. Absorption of omeprazole is rapid, with peak-plasma levels occurring 1-2 hours after the dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3l/kg body weight. Omeprazole is 97% protein bound.

Biotransformation
Omeprazole is completely metabolised, by the cytochrome P450 system (CYP). The major part of metabolism is dependent on the polymorphically expressed CYP 2C19 responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of Omeprazole Sulphone. As a consequence of high affinity of omeprazole to CYP 2C19, there is the potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP 2C19. However due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition Omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of the Asian population lack a functional CYP 2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Elimination
The plasma elimination half life of omeprazole is usually shorter than one hour both after single and repeated oral once daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose- dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and /or it’s metabolites (e.g. the sulphone).

No metabolite has been found to have any effect on gastric acid secretion.

Special Populations

Impaired hepatic function
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once-daily dosing.

Impaired renal function
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

Paediatric patients
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.

5.3 Preclinical safety data

Gastric ECL-cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H_2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these

changes are not from a direct effect of any individual active substance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Content
Drug coating
Sugar spheres (sucrose, maize starch)
Hypromellose
Sodium hydroxide

Barrier coating
Hypromellose

Enteric coating
Methacrylic Acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent (methacrylic acid-ethyl acrylate (1:1), sodium lauryl sulphate, polysorbate 80)
Talc
Titanium dioxide (E171)
Macrogol 6000
Polysorbate 80
Sodium hydroxide

Capsule shell
Shell cap
Iron oxide red (E172), Titanium dioxide (E171), Gelatin, Sodium lauryl sulphate
Shell Body
Titanium dioxide (E171), Gelatin, Sodium lauryl sulphate

Capsule Printing Ink
Shellac, Ammonia solution concentrated, Iron Oxide black (E172), Potassium Hydroxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

HDPE bottle: Do not store above 25°C. Keep the bottle tightly closed in order to protect from moisture

6.5 Nature and contents of container

Round wide mouth white coloured HDPE bottle with white opaque PP screw cap induction sealing line.
7, 14, 15, 21, 28, 30, 50, 56, 60, 84, 100, 112, 200, 500 in bottles
2 x 50
250 (dose dispensing in hospitals – bottle only)

Aluminium/Polyamide/PVC blister.

7, 14, 15, 21, 28, 30, 50, 56, 60, 84, 98, 100, 112, 200, 500 in blisters
2 x 50

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories,
35-36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13,
Ireland.

8 MARKETING AUTHORISATION NUMBER

PA0577/150/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 6th May 2011

10 DATE OF REVISION OF THE TEXT

June 2017