SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Omeprazol Medical Valley 10 mg gastro-resistant capsules, hard
Omeprazol Medical Valley 20 mg gastro-resistant capsules, hard
Omeprazol Medical Valley 40 mg gastro-resistant capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg: Each gastro-resistant capsule contains 10 mg of omeprazole.
20 mg: Each gastro-resistant capsule contains 20 mg of omeprazole.
40 mg: Each gastro-resistant capsule contains 40 mg of omeprazole.

Excipient with known effect
10 mg: Each gastro-resistant capsule contains approximately 6 mg of sucrose.
20 mg: Each gastro-resistant capsule contains approximately 12 mg of sucrose.
40 mg: Each gastro-resistant capsule contains approximately 23 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard (gastro-resistant capsule)

Omeprazol Medical Valley 10 mg gastro-resistant capsules: Hard gelatin capsule with green cap and white body, size 14 mm x 5 mm, containing white to off-white spherical pellets.

Omeprazol Medical Valley 20 mg gastro-resistant capsules: Hard gelatin capsule with blue cap and white body, size 14 mm x 5 mm, containing white to off-white spherical pellets.

Omeprazol Medical Valley 40 mg gastro-resistant capsules: Hard gelatin capsule with white cap and grey body, size 16 mm x 6 mm, containing white to off-white spherical pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Omeprazol Medical Valley gastro-resistant capsules are indicated for:

Adults
- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcers
- 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 oesophagitis
- Long-term management of patients with healed reflux oesophagitis
- Treatment of symptomatic gastro-oesophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

Paediatric use

Children over 1 year of age and ≥ 10 kg

- Treatment of reflux oesophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease.

Children and adolescents over 4 years of age

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

4.2 Posology and method of administration

Posology

Adults

Treatment of duodenal ulcers

The recommended dose in patients with an active duodenal ulcer is Omeprazole Medical Valley 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, treatment should continue for another two weeks. In patients with poorly responsive duodenal ulcer, Omeprazole Medical Valley 40 mg 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 Medical Valley 20 mg 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 40 mg.

Treatment of gastric ulcers

The recommended dose is Omeprazole Medical Valley 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, treatment should continue for another four weeks. In patients with poorly responsive gastric ulcer, Omeprazole Medical Valley 40 mg 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 Medical Valley 20 mg once daily. If needed the dose can be increased to Omeprazole Medical Valley 40 mg 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 and treatment guidelines.

- Omeprazole Medical Valley 20 mg + clarithromycin 500 mg + amoxicillin 1,000 mg, taken together twice daily for one week, or
- Omeprazole Medical Valley 20 mg + clarithromycin 250 mg (alternatively 500 mg) + metronidazole 400 mg (or 500 mg or tinidazole 500 mg), taken together twice daily for one week, or
- Omeprazole Medical Valley 40 mg once daily with both amoxicillin 500 mg and metronidazole 400 mg (or 500 mg or tinidazole 500 mg), three times a day for one week.

If the patient is still *H. pylori* positive after treatment, 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 Medical Valley 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, treatment should continue for

another four weeks.

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

Treatment of reflux oesophagitis
The recommended dose is Omeprazole Medical Valley 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, treatment should continue for another four weeks.
In patients with severe oesophagitis Omeprazole Medical Valley 40 mg once daily is recommended and healing is usually achieved within eight weeks.

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

Treatment of symptomatic gastro-oesophageal reflux disease
The usual dose is Omeprazole Medical Valley 20 mg daily. Patients may respond adequately to 10 mg daily, and therefore the dose should be adjusted individually. If symptom control has not been achieved after four weeks treatment with Omeprazole Medical Valley 20 mg 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 Medical Valley 60 mg once daily. All patients with serious condition and inadequate response to other therapies have been effectively controlled and more than 90% of the patients achieve the desired effect at doses of 20-120 mg daily. When a dose exceeding Omeprazole Medical Valley 80 mg daily is required, the dose should be divided and given twice daily.

Paediatric population

Children over 1 year of age and ≥ 10 kg
Treatment of reflux oesophagitis
Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal 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 years of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed

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

Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal 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 national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and use of antibiotics.

The treatment should be supervised by a specialist physician.

The posology recommendations are as follows:

Weight	Posology
15-30 kg	Combination with two antibiotics: Omeprazole Medical Valley 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administrated together two times daily for one week.
31-40 kg	Combination with two antibiotics: Omeprazole Medical Valley 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated two times daily for one week.
> 40 kg	Combination with two antibiotics: Omeprazole Medical Valley 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administrated two times daily for one week.

Special populations

Renal impairment
Dose adjustment is not needed 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 (> 65 years)
Dose adjustment is not needed in the elderly (see section 5.2).

Method of administration
It is recommended to take Omeprazole Medical Valley capsules in the morning, swallowed whole with half a glass of water. The capsules must not be chewed or crushed since it may impair the effect.

For adults with swallowing difficulties and for children who can drink or swallow semi-solid food
Patients can open the capsule and swallow with half a glass of water or after mixing the contents in a slightly acidic fluid e.g., fruit juice or applesauce, 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. Do not take with milk or carbonated 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 melena) and gastric ulcer is suspected or present, malignancy should be excluded, as treatment may mask 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 20 mg should not be exceeded.

Omeprazole, as 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 fat 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 metabolised through CYP2C19 should be considered. An interaction between clopidogrel and omeprazole has been observed (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be avoided.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors such as omeprazole. The patients had been treated 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 therefore be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the proton pump inhibitor.
For patients expected to be on long term treatment or who take proton pump inhibitors in combination with digoxin or other medicinal products that may cause hypomagnesaemia (e.g. diuretics), magnesium levels should be measured before starting PPI treatment and be monitored during treatment.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported very rarely and rarely, respectively in association with omeprazole 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 known risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture 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 rare 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 the physician should consider stopping Omeprazole Medical Valley. 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 5 days before CgA measurements (see section 5.1). If CgA has not returned to reference levels after the first measurement, the measurements should be repeated 14 days after stopping PPI treatment.

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

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* or *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.

Renal impairment
Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.
Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Excipients
Omeprazol Medical Valley gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per gastro-resistant capsule, that is to say essentially 'sodium-free'.

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 may increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir
The plasma 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 nelvinavir exposure by approximately 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by approximately 75-90%. The interaction may also depend on 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 of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure.
The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoxin
Concomitant treatment with omeprazole (20 mg 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 be 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 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.

Unknown mechanism

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

Tacrolimus
Concomitant administration of omeprazole can 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 CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole plasma 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 plasma levels by increasing omeprazole's rate of metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy
Results from three prospective epidemiological 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.

Fertility
Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Omeprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

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

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with omeprazole treatment (see section 4.4).

Tabulated list of adverse reactions
The following adverse drug reactions have been identified or suspected in clinical trials and post-marketing. None was found to be dose-related.

Adverse reactions listed below are classified according to 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:	Agranulocytosis, pancytopenia
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

SOC/frequency	Adverse reaction
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/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, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
Very rare:	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known:	Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders	
Uncommon:	Fracture of the hip, wrist or spine
Rare:	Arthralgia, myalgia
Very rare:	Muscular weakness
Renal and urinary disorders	
Rare:	Tubulointerstitial nephritis (with possible progression to renal failure)
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 the national reporting system listed in Appendix V.

4.9 Overdose

There is limited information available on the effects of overdoses of omeprazole. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single

oral doses have reached 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 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: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

Mechanism of action
Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and the effect on gastric acid secretion is reversible with 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 the 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.

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 in 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 20 mg 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 oesophagus in patients with gastro oesophageal reflux disease. This effect is dose dependent.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to 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 the major factor in the development of gastritis. *H. pylori* together with gastric acid are the major factors in the development of peptic ulcer disease. *H. pylori* is the 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 healing and long-term

remission of peptic ulcers.

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

Other effects related to acid inhibition
During long-term treatment gastric glandular cysts have been reported in a 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 hospitalised 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 PPI treatment should be discontinued between 5 days and 2 weeks prior to CgA measurement. This is to allow CgA levels that might 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 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 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 H. pylori in children
A randomised, double blind clinical study (Héliot 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 age 4 years old and above with gastritis: *H. pylori* eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

5.2 Pharmacokinetic properties

Absorption
Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after 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 bioavailability from a single oral dose of omeprazole is approximately 40%. After repeated once-daily oral administration, the bioavailability increases to about 60%.

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

Biotransformation
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, 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 sulfone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. 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 Asian populations lack a functional CYP2C19 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 once-daily dosing. Omeprazole is completely eliminated from plasma between two 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.

Linearity/non-linearity
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 dosedependency 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 its metabolites (e.g. the sulfone). No metabolite has been found to have any effect on gastric acid secretion.

Special populations

Hepatic impairment
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.

Renal impairment
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination, 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 population
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

Capsules content:
Sugar spheres: maize starch, sucrose
Magnesium hydroxide
Maize starch
Disodium phosphate
Hypromellose
Sodium laurilsulfate
Mannitol (E421)
Sodium starch glycolate
Talc
Titanium dioxide (E171)
Macrogols
Polysorbate
Methacrylic acid - ethyl acrylate copolymer (1:1) (dry substance)

Composition of hard gelatin capsule
10 mg:
Yellow iron oxide (E172)
Brilliant blue FCF (E133)
Titanium dioxide (E171)
Gelatin

20 mg:
Indigo carmine (E132)
Titanium dioxide (E171)
Gelatin

40 mg:
Black iron oxide (E172)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years for HDPE bottles and PVC/PE/PVDC/Aluminium blister2 years for Aluminium/Aluminium blister

6.4 Special precautions for storage

Blister: Store below 25°C. Store in the original package in order to protect from moisture.

HDPE bottles: This medicine does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Omeprazole Medical Valley 10 mg hard gastro-resistant capsules are packaged in
- Aluminium/Aluminium or PVC/PE/PVDC/Aluminium blister.
  Pack sizes: 7, 14, 15, 16, 28, 30, 32, 35, 42, 50, 56, 60, 90, 98, 100, 105 and 250 capsules.

- HDPE bottle with desiccant (silicagel) container in the polypropylene lid.
  Pack sizes: 7, 14, 15, 16, 28, 30, 32, 50, 56, 60, 90, 98, 100, 105, 120 and 250 capsules

Omeprazole Medical Valley 20 mg hard gastro-resistant capsules are packaged in
- Aluminium/Aluminium or PVC/PE/PVDC/Aluminium blister.
  Pack sizes: 7, 14, 15, 16, 28, 30, 32, 35, 42, 50, 56, 60, 90, 98, 100, 105 and 250 capsules.

- HDPE bottle with desiccant (silicagel) container in the polypropylene lid.
  Pack sizes: 7, 14, 15, 16, 28, 30, 32, 50, 56, 60, 90, 98, 100, 105, 120 and 250 capsules

Omeprazole Medical Valley 40 mg hard gastro-resistant capsules are packaged in
- Aluminium/Aluminium or PVC/PE/PVDC/Aluminium blister.
  Pack sizes: 7, 14, 15, 16, 28, 30, 32, 35, 42, 50, 56, 60, 90, 98, 100, 105 and 250 capsules.

- HDPE bottle with desiccant (silicagel) container in the polypropylene lid.
  Pack sizes: 7, 14, 15, 16, 28, 30, 32, 50, 56, 60, 90, 98, 100, 105, 120 and 250 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

2025-12-04