SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Omeprazole 20 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains omeprazole 20 mg.

Excipient(s) with known effect

Each capsule contains 1.457 mg sodium.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard containing enteric coated pellets

Each capsule consists of blue cap marked with RIA and orange body marked with 20 and contains white to off white pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Treatment of reflux oesophagitis

2. Treatment and prevention of relapse of duodenal and gastric ulcers.

3. Treatment of symptomatic gastro-oesophageal reflux disease.

4. Treatment and prophylaxis of NSAID-associated gastric ulcers and duodenal ulcers in patients at risk.

5. *Helicobacter pylori* eradication: When used with in combination with antibiotics, Omeprazole proves effective in the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.

6. Long-term management of patients with healed reflux oesophagitis

7. 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 gastrooesophageal 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 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 poorly responsive duodenal ulcer Omeprazole 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 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 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. In patients with poorly responsive gastric ulcer Omeprazole 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 20 mg once daily. If needed the dose can be increased to Omeprazole 40 mg once daily.

Helicobacter pylori (Hp) eradication regimens 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 and the following antimicrobial combinations

- Omeprazole 20mg + Amoxicillin1g + clarithromycin 500 mg both twice a day for one week
- Omeprazole 20mg + Clarithromycin 250 mg + metronidazole 400 mg (or tinidazole 500 mg) both twice a day for one week
- Omeprazole 40mg + Amoxicillin 500 mg + metronidazole 400 mg (or 500 mg or tinidazole 500 mg), both three times a day for one week.

In each regimen if symptoms return and the patient tests positive for *Hp*, therapy may be repeated.

Treatment of NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions.

For the treatment of NSAID-associated gastric and duodenal ulcers, the recommended dosage of omeprazole is 20 mg 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 4 weeks treatment period.

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 GI bleeding) the recommended dose is omeprazole 20 mg once daily.

Treatment of reflux oesophagitis

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.

In patients with severe oesophagitis Omeprazole 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 10 mg once daily. If needed, the dose can be increased to Omeprazole 20-40 mg once daily.

Treatment of symptomatic gastro-oesophageal reflux disease

The recommended dose is Omeprazole 20 mg daily. Patients may respond adequately to 10 mg daily, and therefore individual dose adjustment should be considered.

If symptom control has not been achieved after four weeks treatment with Omeprazole 20 mg daily, further investigation is recommended.

Treatment of Zollinger-Ellison syndrome

The initial starting dose is 60 mg omeprazole once a day. The dosage should be adjusted individually, and treatment continued as long as clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20- 120 mg daily. With doses above 80mg daily, 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 gastroesophageal reflux disease

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

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 Helicobacter pylori

When selecting appropriate combination therapy, consideration should be given to official national, regional 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.

The dosage 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 administrated together two times daily for one week.
31–40 kg	Combination with two antibiotics: Omeprazole 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 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 required in patients with impaired renal function. (see section 5.2).

Hepatic impairment

In patients with impaired hepatic function, the 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, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.

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 content in a slightly acidic fluid e.g., fruit juice, 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.

Alternatively, patients can suck the capsule and swallow the pellets with half a glass of water. It is important that the enteric-coated pellets must not be crushed or chewed.

4.3 Contraindications

Hypersensitivity to omeprazole, substituted benzimidazoles or any of the excipients listed in section 6.1.

Omeprazole, like other proton pump inhibitors (PPIs) should 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 when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Co-administration of atazanavir or nelfinavir 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 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 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.

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 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.

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 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.

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

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

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 health care 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.

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 drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

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).

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.

Omeprazole capsules contain less than 1 mmol sodium (23 mg) per 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 might 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 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.

Co-administration of omeprazole (40mg once daily) with atazanavir 300 mg/ritonavir

100mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, Cmax, and Cmin). Increasing the atazanavir dose to 400mg 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.

PPIs including omeprazole should not be co-administered with atazanavir (see section 4.3).

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).

Digoxin:

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

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.

Phenytoin:

Monitoring of patients receiving phenytoin 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.

Cilostazol:

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

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 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 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 serum levels by decreasing omeprazole's rate of metabolism. Concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. A dose adjustment of omeprazole is not regularly required in either of these situations. 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

The analysis of the results from three epidemiological studies (more than 1000 exposed outcomes) has revealed no evidence of adverse events 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 the clinical trials programme for Omeprazole 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

Uncommon ≥ 1/1000 and < 1/100

Rare < 1/1000

Very rare <1/10,000

Not known cannot be estimated from the available data.

System Organ Class	Frequency	adverse event
Blood and lymphatic system disorders	Rare	Leucopenia, Thrombocytopenia
	Very rare:	Agranulocytosis and Pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. Angioedema, Fever, and Anaphylactic shock.
Metabolic and nutritional 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	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Flatulence, 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	Rash, Dermatitis and/or Pruritus, 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	Common	Fracture of the hip, wrist or spine (see section 4.4)
	Rare	Arthritic and myalgic symptoms
	Very rare	Muscular weakness
Renal and urinary disorders	Rare	Interstitial nephritis, Tubulointerstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders		
	Very rare	Gynaecomastia
General	Uncommon	Malaise, Peripheral oedema
disorders and administration site conditions	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 Yellow Card Scheme website at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Rare reports have been received of overdosage with 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 2400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported from overdosage with omeprazole. Also, apathy, depression and confusion have been described in single cases.

The symptoms described in connection to omeprazole overdosage have been transient, and no serious outcome due to omeprazole has been reported. The rate of elimination was unchanged (first order kinetics) with an increase treatment, if needed, is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A02BC01 - Drugs for peptic ulcers and gastro-oesophageal reflux disease - Proton Pump inhibitors.

Omeprazole reduces gastric acid secretion through a unique mechanism of action. It is a specific inhibitor of the gastric proton pump in the parietal cell. It is rapidly acting and produces reversible control of gastric acid secretion with once daily dosing.

Effect on gastric acid secretion

An oral dose of 20 mg once a day produces a rapid and effective inhibition of gastric acid secretion with maximum effect being achieved within 4 days of treatment. In duodenal ulcer patients, a mean decrease of approximately 80% in 24-hour

intragastric acidity is then maintained, with the mean decrease in peak acid output after pentagastrin stimulation being about 70%, twenty-four hours after dosing with Omeprazole 20 mg Capsules.

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. 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

Helicobacter pylori (Hp) is associated with acid peptic disease including duodenal ulcer (DU) and gastric ulcer (GU) in which about 95% and 80% of patients respectively are infected with this bacterium. *Hp* is implicated as a major contributing factor in the development of gastritis and ulcers in such patients. Recent evidence also suggests a causative link between Hp and gastric carcinoma.

Eradication of Hp with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer.

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 an increased frequency of gastric glandular cysts have been reported. These changes are a physiological consequence of pronounced inhibition of acid secretion. The cysts 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 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 data

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 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 (amoxicillin and clarithromycin) 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 + 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.

Site and mechanism of action

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

Pharmacodynamic effects

All pharmacodynamic effects observed are explained by the effect of omeprazole on acid secretion.

5.2 Pharmacokinetic properties

Absorption

Omeprazole is acid labile and is administered orally as enteric-coated pellets in capsules. Absorption takes place in the small intestine and is usually completed within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on the bioavailability.

Distribution

The apparent 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 oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. About 80% of the metabolites are excreted in the urine and the rest in

the faeces.

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 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 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 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 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. Similar findings have been made after treatment with H2-receptor antagonists or subjected to partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition, and not from a direct effect of any individual drug.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres

Sodium starch glycolate

Sodium lauryl sulfate

Povidone K90

Potassium oleate

Oleic acid

Hydroxypropyl methylcellulose 2910 50CPS

Methacrylic acid - ethyl acrylate copolymer (1:1)

Triethyl citrate

Titanium dioxide

Talc

ammonium hydroxide

Capsule
Gelatin
Titanium dioxide (E 171)
iron oxide yellow (E172)
Iron oxide red (E172)
Patent blue V (E131)
purified water
Printing ink
Shellac (E904)
potassium hydroxide (E525)
Titanium dioxide (E171)
Propylene glycol (E1520)
Ammonium hydroxide (E527)
Dehydrated alcohol
Isopropyl alcohol Butyl alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25ºC.
Store in the original package.
Keep the bottle tightly closed.

6.5 Nature and contents of container

HDPE bottle and polypropylene cap with integral silica gel desiccant
Each pack contains 28 capsules.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House
Sarum Hill, Basingstoke
RG21 8SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0994

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/12/2025

10 DATE OF REVISION OF THE TEXT

10/12/2025