Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Omeprazole 20mg Gastro-resistant Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20mg omeprazole.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gastro-resistant capsule.
Capsule with light-flesh coloured body and dark flesh-coloured cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of oesophageal reflux disease, including reflux oesophagitis
- Treatment of duodenal and benign gastric ulcers,
- including those complicating NSAID therapy
- Healing and prophylaxis of NSAID-associated benign gastric ulcers and duodenal ulcers.
- Helicobacter pylori eradication in peptic ulcer disease. Relief of associated dyspeptic symptoms
- Prophylaxis of acid aspiration
- Zollinger-Ellison Syndrome

4.2 Posology and method of administration

Route of Administration
Oral. Capsules should be taken before meals.

Recommended Dosage Schedule
Adults only

Oesophageal Reflux Disease:
For oesophageal reflux disease the usual dose is 20 mg Omeprazole once daily.

In reflux oesophagitis, the majority of the patients are healed after 4 weeks. For those patients not fully healed after the initial course, healing normally occurs during a further 4-8 weeks treatment.

Omeprazole has also been used in a dose of 40 mg once daily in patients with reflux oesophagitis refractory to other therapy. Healing usually occurred within 8 weeks.

Duodenal and Benign Gastric Ulcers:
The usual dose is 20 mg Omeprazole once daily. The majority of the patients are healed after 4-8 weeks. In severe cases, the dose may be increased to 40 mg Omeprazole once daily.

Healing and Prophylaxis of NSAID-Associated Gastric Ulcers and Duodenal Ulcers
For the healing of NSAID-associated gastric ulcers and duodenal ulcers the recommended dosage of Omeprazole is 20 mg once daily. The effectiveness of Omeprazole is not affected by concomitant NSAID treatment. 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. For the prophylaxis of NSAID-associated gastric ulcers and duodenal ulcers, the recommended dosage of Omeprazole is 20 mg once daily.

Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease:
Omeprazole is recommended at a dose of 20 mg twice daily in association with antimicrobial agents as detailed below:

Triple therapy regimens:
Omeprazole and the following antimicrobial combinations; clarithromycin 250 mg and metronidazole 400 mg both twice a day for one week; or amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week. If symptoms return and if the patient is Hp positive therapy may be repeated or one of the alternative regimens can be used. If the patient is Hp negative then see dosage instructions for acid reflux disease.

Dual therapy regimens:
Omeprazole 20 mg twice daily with oral amoxicillin 1g twice daily for two weeks. Alternatively Omeprazole 40 mg once daily and clarithromycin 500 mg three times a day for two weeks.

If symptoms return and if the patient is Hp positive therapy may be repeated or one of the alternative regimens can be used. If the patient is Hp negative then see dosage instructions for acid reflux disease.

To ensure healing in patients with active peptic ulcer disease, see further dosage recommendations for duodenal and benign gastric ulcer.

The following groups are at risk from recurrent ulcer relapse: younger patients (<60 years), those whose symptoms persist for more than 1 year and smokers. These patients will require long-term therapy with Omeprazole 20 mg once daily, reducing to 10mg daily if possible.

The recommended dosage is 20 mg Omeprazole once daily for the prevention of relapse in patients with severe reflux oesophagitis or poorly responsive peptic ulcer. If recurrence occurs, the dose can be increased to 40 mg Omeprazole once daily.

Zollinger-Ellison Syndrome:
The usual initial dose is 60 mg Omeprazole with subsequent adjustment to achieve optimal response in the range of 20-120 mg daily. Doses above 80 mg should be given as a twice daily regimen. Treatment should be continued under specialist supervision as long as clinically indicated.

Prophylaxis of acid aspiration:
For patients considered to be at risk from aspiration of the gastric contents during general anaesthesia, the recommended dosage is Omeprazole 40 mg on the evening before the surgery followed by Omeprazole 40 mg 2-6 hours prior to surgery.

The elderly: Dosage adjustment is not necessary.

Children: In children over 2 years old with severe reflux oesophagitis refractory to conventional treatment, the recommended dosage regimen for healing and symptom relief is:

Weight	Dosage
10-20 kg	Omeprazole 10 mg once daily
>20 kg	Omeprazole 20 mg once daily

for 4 –12 weeks

(For children aged 2-6 years the contents may be dispersed, see section: Patients with swallowing difficulties).

There is limited clinical experience with omeprazole in children aged less than 2 years (see pharmacokinetic properties).

Treatment should be under the supervision of a specialist (paediatrician).

Renal and Liver Disease:
Dose adjustment is not required in patients with impaired renal function.
As plasma half-life of omeprazole is increased in patients with impaired hepatic function, a daily dose of 10-20mg may be sufficient.

Patients with Swallowing Difficulties:
The capsules may be opened and the contents swallowed alone or suspended in juice or yoghurt. The mixture must be taken within 30 minutes of mixing. The contents should not be crushed or chewed.

4.3 Contraindications

Known hypersensitivity to omeprazole or to any of the excipients.
Omeprazole Capsules should not be administered with atazanavir due to an important reduction in atazanavir exposure *(see Section 4.5).*

4.4 Special warnings and precautions for use

When gastric ulcer is suspected the possibility of malignancy should be excluded before treatment with Omeprazole is instituted, as treatment may alleviate symptoms and delay diagnosis.

Omeprazole should be used with caution in patients with severe hepatic dysfunction. Patients should be kept under regular supervision and the daily dose should not exceed 20 mg.

As a matter of good clinical practice, patients requiring long-term maintenance treatment should be reviewed periodically by the physician.

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 or Campylobacter.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine as it contains lactose.

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

4.5 Interaction with other medicinal products and other forms of interaction

Due to decreased intragastric acidity, the absorption of ketoconazole and itraconazole may be decreased during omeprazole treatment as it is during treatment with other acid secretion inhibitors.

Omeprazole undergoes oxidative metabolism, which involves the cytochrome P450 enzyme system, and can delay the elimination of diazepam, phenytoin and warfarin. Monitoring of patients receiving phenytoin or warfarin is recommended and a reduction of phenytoin or warfarin dose may be necessary. However, concomitant treatment with Omeprazole 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with phenytoin. Similarly concomitant treatment with Omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin.

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration. This is considered to be a useful interaction during *H. pylori* eradication. There is no interaction with metronidazole or amoxycillin. These antimicrobials are used to-gether with omeprazole for eradication of Helicobacter pylori. There is no evidence of an interaction with theophylline, caffeine, propranolol, metoprolol, phenacetin, estradiol, cyclosporin, lidocaine, quinidine, erythromycin, budesonide, amoxicillin or antacids. The intake of food reduces the bioavailability of omeprazole: it is recommended to take omeprazole before meals.

There is no evidence of an interaction with piroxicam, diclofenac or naproxen. This is considered useful when patients are required to continue these treatments.

Co-administration of omeprazole 40mg O.D. with atazanavir 300mg/riotnavir 100mg 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. Thus proton pump inhibitors should not be co-administered with atazanavir *(see Section 4.3).*

Interaction with other drugs also metabolised via the cytochrome P450 system cannot be excluded.

4.6 Pregnancy and lactation

Pregnancy
Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child indicating that, Omeprazole can be used if necessary during pregnancy.

Lactation
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

No effects are foreseen.

4.8 Undesirable effects

Omeprazole is well tolerated and adverse reactions have generally been mild and reversible. The following have been reported as adverse events in clinical trials or reported from routine use but in many cases a relationship to treatment with omeprazole has not been established.

The following definitions of frequencies are used:

Common	≥1/100
Uncommon	≥1/1000 and <1/100
Rare	<1/1000

Common

Central and peripheral nervous system:	Headache
Gastrointestinal:	Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence

Uncommon

Central and peripheral nervous system:	Dizziness, paraesthesia, somnolence, insomnia and vertigo.
Hepatic:	Increased liver enzymes.
Skin:	Rash and/or pruritus, urticaria.
Other:	Malaise.

Rare

Central and peripheral nervous system:	Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients.
Endocrine:	Gynaecomastia.
Gastrointestinal:	Dry mouth, stomatitis and gastrointestinal candidiasis.
Haematological:	Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.
Hepatic:	Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure.
Musculoskeleteal:	Arthralgia, muscular weakness and myalgia.
Skin:	Photosensitivity, erythema multiforme, Stevens-*Johnson syndrome*, toxic epidermal necrolysis (TEN), alopecia.
Renal and urinary disorders	Renal dysfunction
Other:	Hypersensitivity reactions e.g. angioedema, fever, bronch-spasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

4.9 Overdose

Rare reports have been received of overdosage with omeprazole. In the literature doses of up to 560mg have been described and occasional reports have been received when single oral doses have reached up to 2400mg 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 increased doses and no specific treatment has been needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A02B C01: Alimentary tract and metabolism, antacids, drugs for treatment of peptic ulcer and flatulence, drugs for treatment of peptic ulcer, proton pump inhibitors, omeprazole.
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.

Oral dosing with 20 mg Omeprazole once daily provides for 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 and output after pentagastrin stimulation being about 70%, twenty-four hours after dosing with Omeprazole.

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.

Omeprazole has been shown to have a bactericidal effect on *Hp* in vitro.

In recent clinical studies using omeprazole 40 mg daily, amoxycillin 1500 mg daily and metronidazole 1200 mg daily for 14 days overall *Hp* eradication rates of 93% and 89% were achieved (96% in metronidazole sensitive isolates).

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 disease, thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged antisecretory treatment.

In recent clinical data in patients with acute peptic ulcer omeprazole *Hp* eradication therapy improved patients' quality of life.

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. No other treatment related mucosal changes have been observed in patients treated continuously with omeprazole for periods up to 5 years.

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.

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

5.2 Pharmacokinetic properties

Absorption and distribution: Omeprazole and omeprazole magnesium are acid labile and are administered orally as enteric-coated granules in capsules or tablets.

Bioequivalence between omeprazole capsules and omeprazole tablets based on the omeprazole plasma concentration-time curve (AUC) has been demonstrated. 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 of omeprazole is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. The intake of food slows the absorption rate of omeprazole and reduces its bioavailability (AUC). The plasma protein binding of omeprazole is about 95%.

Elimination and metabolism: The average half-life of the terminal phase of the plasma concentration-time curve is approximately 40 minutes. There is no change in half-life during treatment. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at a given time.

Omeprazole is entirely metabolised, mainly in the liver. Identified metabolites in plasma are the sulphone, the sulphide and hydroxy-omeprazole, these metabolites have no significant effect on acid secretion. About 80% of the metabolites are excreted in the urine and the rest in the faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function. The area under the plasma concentration-time curve is increased in patients with impaired liver function, but no tendency to accumulation of omeprazole has been found.

Children: Available data from children (1 year and older) suggest that the pharmacokinetics, within the recommended doses are similar to those reported in adults.

5.3 Preclinical safety data

Animal Toxicology: Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole or subjected to partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition, and not from a direct effect of any individual drug.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Sucrose 94 %
Maize starch 6 %
Lactose anhydrous
Hypromellose
Hydroxypropylcellulose
Sodium lauril sulfate
Disodium Phosphate Dihydrate
Hypromellose Phthalate
Diethyl Phthalate

Hard gelatin capsules

Gelatin
Titanium Dioxide (E-171)
Ferric Oxide (E-172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original container.

6.5 Nature and contents of container

Omeprazole 20mg Capsules are stored in polyethylene containers with polypropylene closures and a desiccant.

Omeprazole 20mg Capsules are available in pack sizes of 7 and 28 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0711/090/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of last renewal: 11 November 2005

10 DATE OF REVISION OF THE TEXT

November 2008