Product Information: OMIREN CAPSULES

Prescribing information (Summary of products characteristics):

1.0 Name of the Medicinal Product: OMIREN CAPSULES (Omeprazole BP 20mg (As enteric coated pellets))

2.0 Qualitative and Quantitative composition:
Each capsule contains Omeprazole BP 20 mg
For the full list of excipients, see section 6.1.

3.0 Pharmaceutical form: Capsules
Pink coloured cap/ clear body '2' size capsules filled with Omeprazole enteric coated pellets

4.0 Clinical particular's:

4.1 Therapeutic indication:
Omeprazole 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 in adults
Use in adults
To treat symptoms of GORD such as heartburn and acid regurgitation:
- If your doctor has found that your food pipe (gullet) has been slightly damaged, the recommended dose is 20 mg once a day for 4-8 weeks. Your doctor may tell you to take a dose of 40 mg for a further 8 weeks if your gullet has not yet healed.

- The recommended dose once the gullet has healed is 10 mg once a day.
- If your gullet has not been damaged, the usual dose is 10 mg once a day.

To treat ulcers in the upper part of the intestine (duodenal ulcer):
- The recommended dose is 20 mg once a day for 2 weeks. Your doctor may tell you to take the same dose for a further 2 weeks if your ulcer has not yet healed.
- If the ulcer do not fully heal, the dose can be increased to 40 mg once a day for 4 weeks.

To treat ulcers in the stomach (gastric ulcer):
- The recommended dose is 20 mg once a day for 4 weeks. Your doctor may tell you to take the same dose for a further 4 weeks if your ulcer has not yet healed.
- If the ulcer do not fully heal, the dose can be increased to 40 mg once a day for 8 weeks.

To prevent the duodenal and stomach ulcers from coming back:
- The recommended dose is 10 mg or 20 mg once a day. Your doctor may increase the dose to 40 mg once a day.

To treat duodenal and stomach ulcers caused by NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- The recommended dose is 20 mg once a day for 4–8 weeks.

To prevent duodenal and stomach ulcers if you are taking NSAIDs:
- The recommended dose is 20 mg once a day.

To treat ulcers caused by Helicobacter pylori infection and to stop them coming back:
- The recommended dose is 20 mg Omiren twice a day for one week
- Your doctor will also tell you to take two antibiotics among amoxicillin, clarithromycin and metronidazole.

To treat too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome):
- The recommended dose is 60 mg daily.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for.

Use in children and adolescents

To treat symptoms of GORD such as heartburn and acid regurgitation:
- Children over 1 year of age and with a body weight of more than 10 kg may take Omiren.

The dose for children is based on the child's weight and the doctor will decide the correct dose.

To treat ulcers caused by Helicobacter pylori infection and to stop them coming back:
- Children aged over 4 years may take Omiren. The dose for children is based on the child's weight and the doctor will decide the correct dose.
- Your doctor will also prescribe two antibiotics called amoxicillin and clarithromycin for your child.

Method of administration
It is recommended to take omeprazole capsules in the morning, preferably without food, swallowed whole with half a glass of water. The capsules must not be chewed or crushed.

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food
Patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid e.g., fruit juice or 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. The enteric-coated pellets must not be chewed.

Method of Administration: Oral route.

4.3 Contraindication:
Hypersensitivity to omeprazole, substituted benzimidazoles or to any of the excipients
Omeprazole like other proton pump inhibitors must not be used concomitantly with nelfinavir.

4.4 Special warning and precaution 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 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 B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 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 avoided.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (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), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of 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 infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping Omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 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.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter (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.

4.5 Interactions with other medicinal products and other forms of interactions:

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.

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 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 Cmax 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 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 voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

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

Additional information on special populations:
Not Applicable

Pediatric population:
Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

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.

Breastfeeding
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.

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 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
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
Rare:	Dry mouth, stomatitis, gastrointestinal candidiasis
Not known	Microscopic colitis

Hepatobiliary disorders	
Uncommon:	Increased liver enzymes
Rare:	Hepatitis with or without jaundice
Very rare:	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	
Uncommon:	Dermatitis, pruritus, rash, urticaria
Rare:	Alopecia, photosensitivity
Very rare:	Erythema multiforme, Stevens-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:	Interstitial nephritis
Reproductive system and breast disorders	
Very rare:	Gynaecomastia
General disorders and administration site conditions	
Uncommon:	Malaise, peripheral oedema
Rare:	Increased sweating

Paediatric population

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

4.9 Overdose and Treatment:

There is limited information available on the effects of overdoses of omeprazole in humans. 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 in connection to omeprazole overdose have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Mechanism of action

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

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+ K+-ATPase - the acid pump. This effect on the final step of 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.

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 availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3 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. 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 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

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

Impaired renal function
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.
Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).
Paediatric patients

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

5.3 Preclinical safety data:

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H2-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

Omiren Capsules contains no excipients

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precaution for storage

Do not store above 30˚C, Protect from light and moisture

Keep out of reach of children

6.5 Nature and contents of container

10 Capsules are packed in Alu/Alu strip and such ten strips are packed in a unit carton along with literature insert.

6.6 Special precautions for disposal

No special precaution.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES:

Marketing Authorization Holder:
Rene Industries Ltd
Address: PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

Manufactured by:
Rene Industries Ltd
Address: PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

8. MARKETING AUTHORISATION NUMBER:
Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION:
Not Applicable

10. DATE OF REVISION OF THE TEXT:
Not Applicable

11. DOSIMETRY (IF APPLICABLE):
Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):
Not Applicable