1 NAME OF THE MEDICINAL PRODUCT

Clyomep 40mg Gastro-resistant Capsules Omeprazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contain 40mg of omeprazole

Excipient with known effect: Each capsule contains 233.300mg of sugar spheres (containing sucrose and maize starch)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsule

No.0, containing almost white approximately spherical gastro-resistant granules.

Cap: Green coloured, coded TIL in black.

Body: White, coded $^{OME}_{40}$ in black.

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.

- Zollinger-Ellison syndrome

- Helicobacter eradication: omeprazole should be given in combination with antibiotics for eradication of Helicobacter pylori (Hp) in peptic ulcer disease.

- Prophylaxis of acid aspiration

4.2 Posology and method of administration

Posology

Oesophageal reflux disease including reflux oesophagitis: The usual dosage is 20mg omeprazole once daily. The majority of patients are healed after 4 weeks. Symptom relief is rapid.

For those patients not fully healed after the initial course, healing usually occurs during a further 4-8 weeks treatment.

Omeprazole has also been administered in a dose of 40mg once daily in patients with reflux oesophagitis refractory to other therapy. Healing usually occurred within 8 weeks. Patients can continue at a dosage of 20mg once daily.

Acid reflux disease: For long-term management 10mg omeprazole once daily is recommended, increasing to 20mg if symptoms return.

Duodenal and benign gastric ulcers: The usual dose is 20mg omeprazole once daily. The majority of patients with duodenal ulcer are healed after 4 weeks.

The majority of patients with benign gastric ulcer are healed after 8 weeks. In severe or recurrent cases the dose may be increased to 40mg omeprazole daily. A dosage of 20mg omeprazole once daily is recommended for a long-term therapy in patients with a history of recurrent duodenal ulcer.

For prevention of relapse in patients with duodenal ulcer the recommended dose is 10mg omeprazole once daily, increasing to 20mg once daily, if symptoms return.

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, those with Helicobacter pylori infection. These patients will require initial long-term therapy with 20mg omeprazole once daily, reducing to 10mg once daily, if necessary.

Acid-related dyspepsia: The usual dosage is omeprazole 10mg or 20mg once daily for 2-4 weeks depending on the severity and persistence of symptoms.

For the treatment of NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions: the recommended dosage of omeprazole is 20mg once daily. Symptom resolution is rapid and in most 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, duodenal ulcers, gastroduodenal erosions and dyspeptic symptoms in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment: the only recommended dosage of omeprazole is 20mg once daily.

Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease: Omeprazole is recommended at a dose of 40mg once daily or 20mg twice daily in association with antimicrobial agents.

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

Zollinger-Ellison syndrome: The recommended initial dosage is 60 mg omeprazole once daily. 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 20-120mg daily. With doses above 80mg daily, the dose should be divided and given twice daily.

A limited duration of the omeprazole intake is not foreseen for the treatment of the Zollinger-Ellison syndrome.

Treatment should be continued under specialist supervision as long as clinically indicated.

Special populations

Older people (> 65 years old): Dose adjustment is not required in the older people (see section 5.2).

Paediatric population:

Experience of the use of omeprazole in children is limited. In children over 2 years with severe ulcerating oesophagitis, omeprazole is recommended for healing and symptoms relief within the dose range 0.7-1.4 mg/kg, to a maximum 40mg/day, for 4-12 weeks. Data suggest that approximately 65% of children will experience pain relief with this dose regimen.

Treatment should be initiated by a hospital based paediatrician.

Impaired renal function: Dose adjustment is not required in patients with impaired renal function (see section 5.2).

Impaired hepatic function: In patients with impaired hepatic function a daily dose of 10–20 mg may be sufficient (see section 5.2).

Method of Administration

For reasons of improved absorption, the capsules are to be swallowed whole together with some liquid before meals.

4.3 Contraindications

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

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

Omeprazole like other PPIs should not be administered with atazanavir and 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.

Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors leads to a slightly increased risk of gastrointestinal infections, such as Salmonella and Campylobacter (see section 5.1).

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 discouraged.

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

Omeprazole gastro-resistant tablets contain sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, sucrose-isomaltase insufficiency, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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.

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 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of barbituric acid derivatives should be avoided, since the respiratory depressing effect of fentanyl may be increased.

Tilotrans may exhibit an additive effect with other CNS depressants, e.g.:

opioids

sedatives

hypnotics

general anaesthetics

phenothiazines

anxiolytics and tranquillizer

muscle relaxants

sedating antihistamines

alcoholic beverages

Concomitant use may result in hypoventilation, hypotension, profound sedation, coma or death. Therefore, the use of any of these drugs concomitantly with Tilotrans transdermal patch requires special patient care and observation.

Tilotrans, a high clearance drug, is rapidly and extensively metabolized mainly by CYP3A4.

The concomitant use of transdermal fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, fluconazole, voriconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and transdermal Tilotrans is not recommended, unless the patient is closely monitored (See also Special warnings and precautions for use, Section 4.4.).

Monoamine Oxidase Inhibitors (MAOI)

Tilotrans transdermal patch is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects, *especially in patients with cardiac failure,* or the potentiation of serotoninergic effects, have been reported. Therefore, Tilotrans transdermal patch should not be used within 14 days after discontinuation of treatment with MAOIs.

Concomitant use of mixed agonists/antagonists

The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise

the analgesic effect of Tilotrans and may induce withdrawal symptoms in opioid dependent patients (see also Section 4.4).

<u>Effects of omeprazole on the pharmacokinetics of other active substances</u>

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). 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.

Digoxin

Simultaneous treatment with omeprazole (20 mg daily) and digoxin in healthy subjects leads to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric pH. 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

In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study, it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

The concurrent medication with ketoconazole, itraconazole and with other agents characterized by pH-dependent absorption may lead to an increased gastric pH-value and thus lower the absorption of omeprazole. This also holds true for other acid secretion inhibitors.

Other active substances

The absorption of posaconazole, erlotinib, ketoconazol and itraconazol is significantly reduced and thus clinical efficacy may be impaired. For posaconazol and erlotinib, concomitant use should be avoided.

Active substances *metabolised by CYP2C19*

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. As omeprazole is metabolised in the liver through cytochrome P450 (CYP2C19), it can delay the elimination of diazepam, phenytoin, cilostazol, R-warfarin, and other vitamin K antagonists which are in part substrates for this enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased.

Phenytoin

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

However concomitant treatment with omeprazole daily did not change the blood concentration of phenytoin in patients undergoing continuous treatment with 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.

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of warfarin (or other vitamin K antagonist) dose may be necessary. Concomitant treatment with omeprazole daily did not change coagulation time in patients undergoing continuous treatment with warfarin.

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 and tacrolimus may 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.

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 amoxicillin. These antimicrobials are used together with omeprazole for eradication of Helicobacter pylori.

There is no evidence of an interaction with phenacetin, theophylline, caffeine, propranolol, metoprolol, cyclosporin, lidocaine, quinidine, estradiol, amoxycillin or antacids. The absorption of omeprazole is not affected by alcohol or food.

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

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors CYP2C19 and /or CYP3A4

Concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, or clarithromycin resulted in more than doubling of the omeprazole exposure by decreasing omeprazole's rate of metabolism (As 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). Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC by 15% and 41%, respectively. As high doses of omeprazole have been well-tolerated, 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 prospective 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.

4.7 Effects on ability to drive and use machines

Tilomep 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

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

The following have been identified or suspected as adverse events in 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:

The following definitions of frequencies are used:
Very common (≥ 1/10),
Common ≥ 1/100 to < 1/10 (1-10% of patients)
Uncommon ≥ 1/1000 to < 1/100
Rare ≥1/10,000 to < 1/1000
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. angioedema, fever, anaphylactic shock/reaction
Metabolism and nutrition disorders	
Rare	Hyponatraemia
Not known	Hypomagnesaemia [*See Special warnings and precautions for use (4.4)*]
Psychiatric disorders	
Uncommon	Insomnia
Rare	Reversible mental confusion, agitation, depression
Very rare	Aggression and hallucinations
Nervous System disorders	
Common	Headache
Uncommon	Dizziness, paraesthesia, somnolence, lightheadedness, feeling faint
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, 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,pruritus 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	
Rare	Arthralgia, myalgia
Very rare	Muscular weakness
Uncommon	Fracture of the hip, wrist or spine (see section 4.4)
Renal and urinary disorders	
Rare	Interstitial nephritis
Reproductive system and breast disorders	
Very rare	Gynaecomastia
Rare	Impotence
General disorders and administration site conditions	

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 internet at www.mhra.gov.uk/yellowcard.

4.9 Overdose

There is limited information available on the effects of overdosage with 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 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 increased doses and treatment if needed is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton Pump Inhibitor

ATC code: A02BC

Omeprazole is a proton pump inhibitor. It is a weak base which is converted to its active form, omeprazole sulfenamide in the acidic environment of the parietal cell. It dose-dependently inhibits H^+, K^+-ATPase, the enzyme responsible for the final step of gastric acid secretion. Both basal and stimulated gastric acid secretions are inhibited. The biological half-life of the effect is longer than the elimination half-life of omeprazole.

Suppression of gastric acid secretion stimulates the production of gastrin. Plasma gastrin levels are similar to those observed after a selective vagotomy and return to baseline values 2-4 weeks after cessation of treatment.

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.

5.2 Pharmacokinetic properties

Absorption

Omeprazole is available for oral administration as capsules containing gastro-resistant granules. When the capsule is taken appropriately, the granules are released in the stomach. After the granules leave the stomach the drug is rapidly absorbed in the intestine.

Although the absorption of omeprazole may be delayed by food, the total absorption and bioavailability is not affected by food or antacids, and is approximately 60% following chronic dosing.

Distribution and Metabolism

Omeprazole is highly protein bound (>95%) and completely and rapidly metabolised, undergoing significant first pass metabolism (20%). Approximately 20% of the administered dose is excreted in the faeces and 80% in the urine as metabolites. Three major metabolites have been identified in the plasma and six in the urine. The primary mechanism of metabolism is via the cytochrome P450 enzymes, and is subject to an important drug metabolising polymorphism as it is a substrate for CYP2C19. Slow metabolisers deficient in CYP2C19 will experience greater plasma concentration and AUC and a prolonged elimination half-life.

Excretion

The primary and secondary metabolites are excreted primarily in the faeces (20%) by biliary secretion, and in urine (80%).

Pharmacokinetics in Specific Patient Groups

Older people: In the older people, the elimination half-life may be slightly prolonged and the AUC increased twofold.

Renal Insufficiency: Omeprazole is completely metabolised in the liver and none of the metabolites appear to possess functional activity. While renal excretion of inactive metabolites is reduced, a compensatory increase in biliary/faecal excretion appears to occur. Haemodialyasis does not appear to affect omeprazole pharmacokinetics.

Hepatic Insufficiency: Omeprazole is completely metabolised by the liver and in patients with liver disease the bioavailability is increased to almost a 100%, the AUC increased by 9 fold and the plasma elimination half-life by 4 fold. However the elimination half-life is still considerably shorter than the dosing interval and no drug accumulation should be expected during chronic dosing.

5.3 Preclinical safety data

Gastric ECL-cell hyperplasia and carcinoids have been observed in lifelong studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition, and not from a direct effect of any

individual drug. Similar findings have been made after treatment with H2-receptor antagonists, proton pump inhibitors and after partial fundectomy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium laurilsulfate

Crospovidone

Sugar spheres 18/20, containing sucrose and maize starch

Hard fat

Glyceryl monostearate 40-50

Talc

Hypromellose 5cps

Talc (micronized)

Titanium dioxide (E171)

Methacrylic acid-ethyl acrylate copolymer (1:1)

Triethyl citrate

Dimeticone

Gelatin

Colouring agents

Titanium dioxide (E171)

Indigo carmine (E132)

Quinoline yellow (E104)

Printing ink 1012-black:

Shellac

Black iron oxide (E172)

Soya lecithin

Antifoam DC 1510

6.2 Incompatibilities

Not applicable

6.3 Shelf life

6 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container. Keep the container tightly closed.

6.5 Nature and contents of container

High density polyethylene container with tamper evident polypropylene screw cap and dessicant insert containing 7 capsules.

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clydesdale Pharma Ltd

Unit 3-5 Campbell Court

Campbell Road

Tadley

RG26 5EG

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 51718/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 17/09/2008

Date of renewal: 23/03/2009

10 DATE OF REVISION OF THE TEXT

14/03/2025