Public Assessment Report

Mutual Recognition Procedure

Emozul 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0108/001-002/MR

Esmep 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0109/001-002/MR

Esmera 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0110/001-002/MR

Esomeprazol Hygia 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0111/001-002/MR

Esora 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0112/001-002/MR

Faras 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0113/001-002/MR

Peros 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0114/001-002/MR

Prazos 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0115/001-002/MR

Sempra 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0116/001-002/MR

Zaros 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0117/001-002/MR

Esomeprazole magnesium dihydrate

SI/H/0108-0117/001-002/MR

Table of Contents

Module 1: Information about the initial procedure

Product Name	**SI/H/0108/001-002/MR:** Emozul 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0109/001-002/MR**: Esmep 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0110/001-002/MR**: Esmera 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0111/001-002/MR:** Esomeprazol Hygia 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0112/001-002/MR:** Esora 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0113/001-002/MR:** Faras 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0114/001-002/MR:** Peros 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0115/001-002/MR:** Prazos 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0116/001-002/MR:** Sempra 20 mg and 40 mg gastro-resistant capsules, hard **SI/H/0117/001-002/MR:** Zaros 20 mg and 40 mg gastro-resistant capsules, hard
Type of application	Abridged, Article 10.1
Active Substance	Esomeprazole magnesium dihydrate
Form	Gastro-resistant capsule, hard
Strength	20 mg & 40 mg
MA Holder	HYGIA družba za proizvodnjo in promet zdravil na debelo, Novo mesto d.o.o. Foersterjeva ulica 10, 8000 Novo mesto Slovenia
RMS	SI
Procedure-number and CMS	**SI/H/0108/001-002/MR**: BE, CY, DE, EL, IE, IT, NL and SE **SI/H/0109/001-002/MR:** UK

	SI/H/0110/001/MR: AT, BE, DE, DK, EE, FI, HU, IT, LT, LU, LV, NL, NO, PL, SE and SK **SI/H/0110/002/MR:** AT, DE, DK, EE, FI, HU, IT, LT, LU, LV, NL, NO, PL, SE and SK. **SI/H/0111/001-002/MR**: DE **SI/H/0112/001-002/MR:** DE, ES and PT **SI/H/0113/001-002/MR:** DE **SI/H/0114/001-002/MR:** DE and IT **SI/H/0115/001-002/MR**: DE, IT, and NL **SI/H/0116/001-002/MR:** DE and ES **SI/H/0117/001-002/MR:** DE, ES and PT
Timetable	Start: March 31, 2010 End: June 29, 2010

Module 2: Summary of Product Characteristcs

1. NAME OF THE MEDICINAL PRODUCT

<Product name> 20 mg gastro-resistant capsules, hard
<Product name> 40 mg gastro-resistant capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant capsule, hard, contains 20 mg esomeprazole (as esomeprazole magnesium dihydrate).

Each gastro-resistant capsule, hard, contains 40 mg esomeprazole (as esomeprazole magnesium dihydrate).

Excipient:

	20 mg gastro-resistant capsules, hard	40 mg gastro-resistant capsules, hard
sucrose	28.46–32.56 mg	56.93–65.11 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant capsule, hard.
20 mg: the body and the cap are slightly pink in colour; the capsules contain white to almost white pellets.
40 mg: the body and the cap are off-pink in colour; the capsules contain white to almost white pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name> capsules are indicated for:

Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and
- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers

Patients requiring continued NSAID therapy
Healing of gastric ulcers associated with NSAID therapy.

Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

4.2 Posology and method of administration

The capsules should be swallowed whole with some water. The capsules should not be chewed or crushed.

For patients who have difficulty in swallowing, the capsules can also be opened and the pellets mixed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Drink the water with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the capsules can be opened and pellets mixed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested before use (see section 6.6).

Adults and adolescents from the age of 12 years
Gastroesophageal Reflux Disease (GERD)

- treatment of erosive reflux esophagitis
  40 mg once daily for 4 weeks.
  An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.

- long-term management of patients with healed esophagitis to prevent relapse
  20 mg once daily.

- symptomatic treatment of gastroesophageal reflux disease (GERD)
  20 mg once daily in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. In adults, an on demand regimen taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

Adults
In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and

- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.
  20 mg <Product name> with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Patients requiring continued NSAID therapy
Healing of gastric ulcers associated with NSAID therapy: The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk: 20 mg once daily.

Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers
40 mg once daily for 4 weeks after IV induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

The recommended initial dosage is <Product name> 40 mg twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 to 160 mg esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Children below the age of 12 years
<Product name> should not be used in children younger than 12 years since no data is available.

Impaired renal function
Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section 5.2).

Impaired hepatic function
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg <Product name> should not be exceeded (see section 5.2).

Elderly
Dose adjustment is not required in the elderly.

Do not eat the desiccant capsule provided in the container.

4.3 Contraindications

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any of the excipients.

Esomeprazole 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 melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with <Product name> may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see section 4.5).

When prescribing esomeprazole for eradication of *Helicobacter pylori* possible active substance interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other medicinal products metabolised via CYP3A4 such as cisapride.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* (see section 5.1).

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Special information about some of the ingredients

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of esomeprazole on the pharmacokinetics of other active substances

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole might increase or decrease the absorption of active substances if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). 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 with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36-39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once daily had no effect on the exposure of lopinavir (with concomitant ritonavir). Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

Active substances metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with active substances metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these active substances may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy. Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15% and 41%, respectively.

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc

interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see also section 4.4).

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other active substances on the pharmacokinetics of esomeprazole
Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_{τ} by 280%. A dose adjustment of esomeprazole 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.

4.6 Pregnancy and lactation

For esomeprazole, clinical data on exposed pregnancies are insufficient. With the racemic mixture, omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore <Product name> should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

<Product name> has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related.

The reactions are classified according to frequency:
- 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)

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

Uncommon: Peripheral oedema
Rare: Hyponatraemia

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
Uncommon: Dry mouth
Rare: Stomatitis, gastrointestinal candidiasis

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)

Musculoskeletal, connective tissue and bone disorders
Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site conditions
Rare: Malaise, increased sweating

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proton pump inhibitors
ATC Code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Site and mechanism of action
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion
After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Therapeutic effects of acid inhibition
Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.
After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory active substances for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) were randomized to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression The occurrence of rebleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group 7.7% vs 13.6%.

Other effects related to acid inhibition
During treatment with antisecretory active substances serum gastrin increases in response to the decreased acid secretion.

An increased number of ECL cells (enterochromaffin-like cells), possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory active substances gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

5.2 Pharmacokinetic properties

Absorption and distribution
Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively.The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Metabolism and excretion
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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 esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent compound is found in urine.

Special patient populations
Approximately 2.9 ± 1.5% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%.
These findings have no implications for the posology of esomeprazole.

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of esomeprazole.

Impaired organ function
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Paediatric
Adolescents 12-18 years:
Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma concentration (t_{max}) in 12 to18 year-olds was similar to that in adults for both esomeprazole doses.

5.3 Preclinical safety data

Preclinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets in the capsule core:
Sugar spheres (sucrose and maize starch)
Povidone
Sodium laurilsulfate
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol
Talc (E553b)

Magnesium carbonate, heavy
Polysorbate 80 (E433)
Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent

Capsule shell:
Gelatin (E441)
Titanium dioxide (E171)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack/HDPE container: 18 months.
HDPE container: after first opening, the product should be used within 3 months.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Blister pack
Store in the original package in order to protect from moisture.

HDPE container
Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Blister pack (Al/Al foil + desiccant film): 7, 10, 14, 15, 28, 30, 50, 56, 60, 90, 98 and 100 gastro-resistant capsules, hard, in a box.

HDPE container, PP closure with a desiccant: 98 gastro-resistant capsules, hard, and a desiccant capsule, in a box. Do not eat the desiccant capsule provided in the container.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Administration through gastric tube
1. Open the capsule and empty the pellets into an appropriate syringe and fill the syringe with approximately 25 ml water and approximately 5 ml air.
   For some tubes, dispersion in 50 ml water is needed to prevent the pellets from clogging the tube.
2. Immediately shake the syringe to evenly distribute the granules throughout the suspension.
3. Hold the syringe with the tip up and check that the tip has not clogged.
4. Attach the syringe to the tube whilst maintaining the above position.
5. Shake the syringe and position it with the tip pointing down. Immediately inject 5 – 10 ml into the tube. Invert the syringe after injection and shake (the syringe must be held with the tip pointing up to avoid clogging of the tip)
6. Turn the syringe with the tip down and immediately inject another 5 – 10 ml into the tube. Repeat this procedure until the syringe is empty.

7. Fill the syringe with 25 ml of water and 5 ml of air and repeat step 5 if necessary to wash down any sediment left in the syringe. For some tubes, 50 ml water is needed.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

To be completed nationally.

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

<Product name> 20 mg gastro-resistant capsules, hard
<Product name> 40 mg gastro-resistant capsules, hard
Esomeprazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT <PRODUCT NAME> IS AND WHAT IT IS USED FOR

<Product name> contains a medicine called esomeprazole magnesium dihydrate. This belongs to a group of medicines called "proton pump inhibitors". They work by reducing the amount of acid that your stomach produces.

<Product name> is used to treat the following conditions:
- Gastro-esophageal reflux disease (GERD). This is where acid from the stomach escapes into the gullet (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
- Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called "*Helicobacter pylori*". If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.
- Stomach ulcers caused by medicines called NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). <Product name> can also be used to stop stomach ulcers from forming if you are taking NSAIDs.
- Too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome).
- Prolonged treatment after prevention of rebleeding of ulcers with intravenous esomeprazole.

2. BEFORE YOU TAKE <PRODUCT NAME>

Do not take <Product name> if:
- You are allergic (hypersensitive) to esomeprazole or any of the other ingredients of this medicine (listed in Section 6: Further information).
- You are allergic to other proton pump inhibitor medicines.
- You are taking a medicine containing nelfinavir (used to treat HIV).

Do not take <Product name> if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking <Product name>.

Take special care with <Product name>
Check with your doctor or pharmacist before taking <Product name> if:
- You have severe liver problems.
- You have severe kidney problems.

<Product name> may hide the symptoms of other diseases. **Therefore, if any of the following happen to you before you start taking <Product name> or while you are taking it, talk to your doctor straight away:**
- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).

If you have been prescribed <Product name> "on demand" you should contact your doctor if your symptoms continue or change in character.

If diarrhoea occurs during the treatment with <Product name> contact your doctor immediately, as treatment with proton pump inhibitors may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Taking other medicines
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines. This includes medicines that you obtained without a prescription. This is because <Product name> can affect the way some medicines work and some medicines can have an effect on <Product name>.

Do not take <Product name> Capsules if you are taking a medicine containing **nelfinavir** (used to treat HIV).

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Atazanavir (used to treat HIV).
- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Citalopram, imipramine or clomipramine (used to treat depression).
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop taking <Product name>.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking <Product name>.
- Cisapride (used for indigestion and heartburn).

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as <Product name> to treat ulcers caused by *Helicobacter pylori* infection, it is very important that you tell your doctor if you are taking any other medicines.

Pregnancy and breast-feeding
Before taking <Product name>, tell your doctor if you are pregnant or trying to get pregnant. Ask your doctor or pharmacist for advice before taking any medicine. Your doctor will decide whether you can take <Product name> during this time.
It is not known if <Product name> passes into breast milk. Therefore, you should not take <Product name> if you are breastfeeding.

Taking <Product name> with food and drink
You can take your capsules with food or on an empty stomach.

Driving and using machines
<Product name> is not likely to affect you being able to drive or use any tools or machines.

Important information about some of the ingredients of <Product name>
<Product name> gastro-resistant capsules contain sucrose, which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. HOW TO TAKE <PRODUCT NAME>

Always take <Product name> exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- <Product name> gastro-resistant capsules are not recommended for children less than 12 years old.
- If you are taking this medicine for a long time, your doctor will want to monitor you (particularly if you are taking it for more than a year).
- If your doctor has told you to take this medicine as and when you need it, tell your doctor if your symptoms change.

Taking this medicine
- You can take your capsules at any time of the day.
- You can take your capsules with food or on an empty stomach.
- Swallow your capsules whole with a drink of water. Do not chew or crush the capsules. This is because the capsules contain coated pellets which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

What to do if you have trouble swallowing the capsules
- If you have trouble swallowing the capsules:
  - Open the capsule and empty the pellets into half a glass of still (non-fizzy) water. Do not use any other liquids.
  - Then drink the mixture straight away or within 30 minutes. Always stir the mixture just before drinking it.
  - To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. The solid pieces contain the medicine - do not chew or crush them.
- If you cannot swallow at all, the pellets can be mixed with some water and put into a syringe. They can then be given to you through a tube directly into your stomach (′gastric tube′).

How much to take
- Your doctor will tell you how many capsules to take and how long to take them for. This will depend on your condition, how old you are and how well your liver works.
- The usual doses are given below.

To treat heartburn caused by gastro-esophageal reflux disease (GERD):
Adults and children aged 12 or above:
- If your doctor has found that your food pipe (gullet) has been slightly damaged, the usual dose is one <Product name> 40 mg gastro-resistant capsule once a day for 4 weeks. Your doctor may tell you to take the same dose for a further 4 weeks if your gullet has not yet healed.
- The usual dose once the gullet has healed is one <Product name> 20 mg gastro-resistant capsule once a day.
- If your gullet has not been damaged, the usual dose is one <Product name> 20 mg gastro-resistant capsule each day. Once the condition has been controlled, your doctor may tell you to take your medicine as and when you need it, up to a maximum of one <Product name> 20 mg gastro-resistant capsule each day.
- If you have severe liver problems, your doctor may give you a lower dose.

To treat ulcers caused by *Helicobacter pylori* infection and to stop them coming back:
- Adults aged 18 or above: the usual dose is one <Product name> 20 mg gastro-resistant capsule twice a day for one week.
- Your doctor will also tell you to take antibiotics called amoxicillin and clarithromycin.

To treat stomach ulcers caused by NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one <Product name> 20 mg gastro-resistant capsule once a day for 4 to 8 weeks.

To prevent stomach ulcers if you are taking NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):
- Adults aged 18 and above: the usual dose is one <Product name> 20 mg gastro-resistant capsule once a day.

To treat too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome):
- Adults aged 18 and above: the usual dose is one <Product name> 40 mg gastro-resistant capsule twice a day.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for. The maximum dose is 80 mg twice a day.

Prolonged treatment after prevention of rebleeding of ulcers with intravenous esomeprazole:
- Adults aged 18 and above: the usual dose is one <Product name> 40 mg capsule once a day for 4 weeks.

If you take more <Product name> than you should
If you take more <Product name> than prescribed by your doctor, talk to your doctor or pharmacist straight away.

If you forget to take <Product name>
- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose.
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, <Product name> can cause side effects, although not everybody gets them.

Side effects are classified into the following groups in order of frequency:

Very common:	Affects more than 1 user in 10
Common:	Affects 1 to 10 users in 100
Uncommon:	Affects 1 to 10 users in 1,000
Rare:	Affects 1 to 10 users in 10,000
Very rare:	Affects less than 1 user in 10,000
Not known:	Frequency cannot be estimated from available data

If you notice any of the following serious side effects, stop taking <Product name> and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).

- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be "Stevens-Johnson syndrome" or "toxic epidermal necrolysis".
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

These effects are rare, affecting less than 1 in 1,000 people.

Other side effects include:

Common
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Uncommon
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Dry mouth.
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.

Rare
- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- An inflammation of the inside of the mouth.
- An infection called "thrush" which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pains (arthralgia) or muscle pains (myalgia).
- Generally feeling unwell and lacking energy.
- Increased sweating.

Very rare
- Changes in blood count including agranulocytosis (lack of white blood cells).
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Severe kidney problems.
- Enlarged breasts in men.

<Product name> may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis)

can be ruled out by a blood test. It is important for you to give information about your medication at this time.

Do not be concerned by this list of possible side effects. You may not get any of them. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE <PRODUCT NAME>

Keep out of the reach and sight of children.

Do not use <Product name> after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions.

Blister pack
Store in the original package in order to protect from moisture.

HDPE container
Keep the container tightly closed in order to protect from moisture.
After first opening of the container, the product should be used within 3 months.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What <Product name> contains
The active substance is esomeprazole. Each gastro-resistant capsule, hard, contains 20 mg or 40 mg esomeprazole (as esomeprazole magnesium dihydrate).
The other ingredients are sugar spheres (sucrose and maize starch), povidone, sodium laurilsulfate, poly(vinyl alcohol), titanium dioxide (E171), macrogol, talc (E553b), heavy magnesium carbonate, polysorbate 80 (E433) and methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent in pellets in the capsule, and gelatine (E441), titanium dioxide (E171) and red iron oxide (E172) in the capsule shell.

What <Product name> looks like and contents of the pack
The body and cap of the 20 mg gastro-resistant capsules, hard, are slightly pink. The capsules contain white to almost white pellets.
The body and cap of the 40 mg gastro-resistant capsules, hard, are off-pink. The capsules contain white to almost white pellets.
The capsules are available in boxes of 7, 10, 14, 15, 28, 30, 50, 56, 60, 90, 98 and 100 capsules in blister packs, and boxes of 98 capsules and a desiccant capsule in HDPE containers. Do not eat the desiccant capsule provided in the container.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
To be completed nationally.

Manufacturer
KRKA, tovarna zdravil, d. d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

This leaflet was last approved in
<To be completed nationally>

Module 4: Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX/for blisters

1. NAME OF THE MEDICINAL PRODUCT

Product name 20 mg gastro-resistant capsules, hard
Product name 40 mg gastro-resistant capsules, hard

Esomeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant capsule, hard, contains 20 mg esomeprazole (as esomeprazole magnesium dihydrate).
Each gastro-resistant capsule, hard, contains 40 mg esomeprazole (as esomeprazole magnesium dihydrate).

3. LIST OF EXCIPIENTS

Contains sucrose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 gastro-resistant capsules, hard
10 gastro-resistant capsules, hard
14 gastro-resistant capsules, hard
15 gastro-resistant capsules, hard
28 gastro-resistant capsules, hard
30 gastro-resistant capsules, hard
50 gastro-resistant capsules, hard
56 gastro-resistant capsules, hard
60 gastro-resistant capsules, hard
90 gastro-resistant capsules, hard
98 gastro-resistant capsules, hard
100 gastro-resistant capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Product name 20 mg
Product name 40 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER/ Al/Al-foil + desiccant

1. NAME OF THE MEDICINAL PRODUCT

Product name 20 mg gastro-resistant capsules, hard
Product name 40 mg gastro-resistant capsules, hard

Esomeprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX/for HDPE container

1. NAME OF THE MEDICINAL PRODUCT

Product name 20 mg gastro-resistant capsules, hard
Product name 40 mg gastro-resistant capsules, hard

Esomeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant capsule, hard, contains 20 mg esomeprazole (as esomeprazole magnesium dihydrate).
Each gastro-resistant capsule, hard, contains 40 mg esomeprazole (as esomeprazole magnesium dihydrate).

3. LIST OF EXCIPIENTS

Contains sucrose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 gastro-resistant capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening of the container, the product should be used within 3 months.

9. SPECIAL STORAGE CONDITIONS

Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Product name 20 mg
Product name 40 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL

1. NAME OF THE MEDICINAL PRODUCT

Product name 20 mg gastro-resistant capsules, hard
Product name 40 mg gastro-resistant capsules, hard

Esomeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant capsule, hard, contains 20 mg esomeprazole (as esomeprazole magnesium dihydrate).
Each gastro-resistant capsule, hard, contains 40 mg esomeprazole (as esomeprazole magnesium dihydrate).

3. LIST OF EXCIPIENTS

Contains sucrose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

98 gastro-resistant capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening of the container, the product should be used within 3 months.

9. SPECIAL STORAGE CONDITIONS

Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Module 5: Scientific discussion during the initial procedure

Public Assessment Report

Scientific discussion

Emozul 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0108/001-002/MR

Esmep 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0109/001-002/MR

Esmera 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0110/001-002/MR

Esomeprazol Hygia 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0111/001-002/MR

Esora 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0112/001-002/MR

Faras 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0113/001-002/MR

Peros 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0114/001-002/MR

Prazos 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0115/001-002/MR

Sempra 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0116/001-002/MR

Zaros 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0117/001-002/MR

This module reflects the scientific discussion for the approval of Esomeprazole 20 mg and 40 mg gastro-resistant capsules, hard. The procedure was finalised at June 29, 2010. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the SI has granted a Marketing Authorisation for the medicinal products containing Esomeprazole: Emozul, Esmep, Esmera, Esomeprazol Hygia, Esora, Faras, Peros, Prazos, Sempra and Zaros in the treatment of:

Gastroesophageal Reflux Disease (GERD)
- Treatment of erosive reflux esophagitis
- Long-term management of patients with healed esophagitis to prevent relapse
- Symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and
- Healing of *Helicobacter pylori* associated duodenal ulcer and
- Prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers

Patients requiring continued NSAID therapy
- Healing of gastric ulcers associated with NSAID therapy
- Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk

Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers
Treatment of Zollinger Ellison Syndrome

In this Public Assessment Report, the common name Esomeprazole or Esomeprazole Hygia will be used. However this report applies for the applications of Emozul (SI/H/0108/001-002/MR), Esmep (SI/H/0109/001-002/MR), Esmera (SI/H/0110/001-002/MR), Esomeprazol Hygia (SI/H/0111/001-002/MR), Esora (SI/H/0112/001-002/MR), Faras (SI/H/0113/001-002/MR), Peros (SI/H/0114/001-002/MR), Prazos (SI/H/0115/001-002/MR), Sempra (SI/H/0116/001-002/MR) and Zaros (SI/H/0117/001-002/MR). These medicinal products were granted national Marketing Authorisations in Slovenia in October 2009 and January 2010, as generic versions of Nexium 20 mg and 40 mg gastro-resistant tablets, authorised in Slovenia since September 3, 2002 by AstraZeneca UK Ltd.

Pharmacotherapeutic group: Proton pump inhibitors.
ATC Code: A02BC05

Esomeprazole is the S-isomer of omeprazole. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity; however, the S-isomer has the highest bioavailability and oral potency in inhibiting gastric acid secretion in human, owning to stereoselective metabolism of omeprazole.

As with other Proton Pump Inhibitors, esomeprazole suppresses gastric acid secretion from gastric parietal cells. As a weak base, esomeprazole is concentrated in the acidic environment of the parietal cells, where it is protonated and converted to the active inhibitor, achiral sulphenamide. A reaction with specific cysteines results in the inhibition of the proton pump, blocking the final step in acid production and increase intragastric pH. Both basal and stimulated acid secretion is severely decreased due to the acid pump blockade.

With Slovenia as the Reference Member State in these Mutual Recognition Procedures, the Marketing Authorisation Holder, Hygia Novo Mesto, d.o.o. applied for the Marketing Authorisations for esomeprazole gastro-resitant capsules, hard in the following CMS':

SI/H/0108/001-002/MR: BE, CY, DE, EL, IE, IT, NL and SE
SI/H/0109/001-002/MR: UK

SI/H/0110/001/MR: AT, BE, DE, DK, EE, FI, HU, IT, LT, LU, LV, NL, NO, PL, SE and SK
SI/H/0110/002/MR: AT, DE, DK, EE, FI, HU, IT, LT, LU, LV, NL, NO, PL, SE and SK
SI/H/0111/001-002/MR: DE
SI/H/0112/001-002/MR: DE, ES and PT
SI/H/0113/001-002/MR: DE
SI/H/0114/001-002/MR: DE and IT
SI/H/0115/001-002/MR: DE, IT, and NL
SI/H/0116/001-002/MR: DE and ES
SI/H/0117/001-002/MR: DE, ES and PT

The legal basis for these applications was in accordance with article 10(1) of amended Directive 2001/83/EC in force and the legal basis has been adequately justified by the applicant.

The reference medicinal product (brand leader) referred to as authorised not less than 6/10 years in EEA is Nexium, gastro-resistent tablets, authorised in Sweden since March 10, 2000 by Astra Zeneca AB. Essential similarity with the Nexium mups 20 mg and 40 mg gastro-resistant tablets, AstraZeneca GmbH, taken from the German Market is claimed based on three bioequivalence studies. The BE studies were carried out in accordance with the relevant CHMP Note for Guidance on Modified Release Oral and Transdermal Dosage Forms and the relevant CHMP Guideline on the Investigation of Bioequivalence.

No formal Environmental Risk Assessment has been provided. The applicant has justified the absence adequately.

The RMS has been assured that acceptable standards of GMP are in place for these product types at site responsible for the manufacture and assembly of these products prior to granting their national authorisations.

For manufacturing site within the Community, the RMS has accepted current manufacturer authorisations and GMP certificates issued by inspection service of the competent authority as certification that acceptable standards of GMP are in place at that site.

For the active substance manufacture, Qualified Person of the manufacturer of finished product and the batch releasing company confirmed that the quality of their own product esomeprazole magnesium API complies with the EU GMP-conforming production. In addition, for the active substance the Manufacturing Authorisation and certificate of GMP compliance was provided.

The clinical study site and the analytical site were inspected in May 2009 by the Slovenian Authorities. The inspection revealed no critical or major findings.

The submitted bioequivalence studies were claimed to be performed according to GCP and GLP principles and the Declaration of Helsinki.

The Mutual Recognition Procedures were successfully completed at day 90 (June 29, 2010).

II. QUALITY ASPECTS

II.1 Introduction

The finished product is gastro-resistant capsule, hard containing 20 mg or 40 mg of esomeprazole in the form of esomeprazole magnesium dihydrate.

Esomeprazole 20 mg gastro-resistant capsules, hard appear as slightly pink capsules (body and cap) filled with white to almost white pellets. Esomeprazole 40 mg gastro-resistant capsules, hard appear as off-pink capsules (body and cap) filled with white to almost white pellets.

The product is intended for oral administration and is proposed for marketing in Al-Al foil blisters (laminated OPA/Al/PE+desiccant film - aluminium/PE foil) in pack sizes of 7, 10, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100 hard gastro-resistant capsules, and in HDPE containers with 98 hard gastro-resistant capsules.

The excipients in the capsules are:

Pellets in the capsule core:
Sugar spheres (sucrose and maize starch)
Povidone
Sodium laurilsulfate
Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol
Talc (E553b)
Magnesium carbonate, heavy
Polysorbate 80 (E433)
Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent

Capsule shell:
Gelatin (E441)
Titanium dioxide (E171)
Red iron oxide (E172)

II.2 2.2 Drug Substance

INN: Esomeprazole
Chemical name(s): 5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium dihydrate

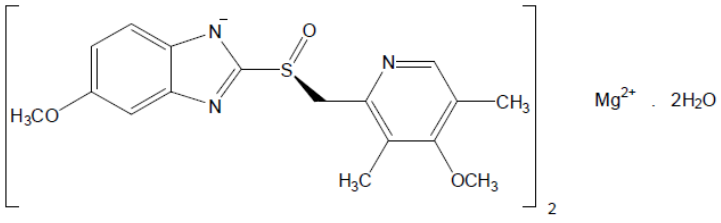
5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt (2:1), dihydrate

bis(5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1Hbenzimidazole-1-yl) magnesium dihydrate

Magnesium bis[5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2- pyridinyl)methyl]sulfinyl]-1H-benzimidazol-1-ide] dihydrate
Other non-proprietary name: Esomeprazole magnesium dihydrate

CAS No.: 217087-10-0

S.1.2 Structure



Molecular formula: $C_{34}H_{36}MgN_6O_6S_2 \cdot 2\ H_2O$

Molecular weight: 749.15

Esomeprazole magnesium dihydrate is not described in the European Pharmacopoeia. The documentation on the active substance esomeprazole magnesium dihydrate is presented as an ASMF in CTD format and satisfactory letters of access are provided. ASMF holder is the same as the manufacturer of the finished product.
Manufacturing process is adequately described and critical steps were recognized and evaluated.
Specifications and test methods for the quality control of active substance are adequately drawn up. The manufacturing process produces consistently the same crystalline form of Esomeprazole magnesium dihydrate. The control of polymorphic form is performed routinely.
Potential impurities have been satisfactorily described and limits for impurities and residual solvents are set according to CPMP/ICH guidelines and Ph. Eur. The route of synthesis was evaluated for the presence of genotoxic impurities. The analytical procedures are validated.
Stability studies in accordance with the relevant ICH/CHMP guidelines have been performed with the active substance. No significant changes in any parameters were observed. The proposed retest period of 2 years when stored in the original packing in order to protect from light is justified.

II.3 Medicinal Product

The finished products are gastro-resistant capsules, hard containing 20 mg or 40 mg of esomeprazole in the form of esomeprazole magnesium dihydrate. The purpose of development was to attain a bioequivalent and stable gastro-resistance capsule formulation with the same active moiety that is comparable in performance to the reference product Nexium mups gastro-resistant tablets from AstraZeneca AB.
The excipients used are Ph. Eur., and are regularly used in the manufacture of solid dosage forms. The choice of excipients is justified and their functions explained.
The development of the product has been adequately described. Dissolution and impurity profile data of proposed product are comparable to the brand leader. The selection of dissolution media, gastro-resistant conditions and dissolution conditions are justified.
The manufacturing process of gastro-resistant capsules is a non-standard process. Adequate in-process controls and process validation data on production scale batches of pellets and encapsulated product are sufficient to demonstrate the adequacy of the manufacturing process.
The release and shelf-life specifications of the finished product and in-process controls cover all essential quality aspects required for capsules by the Ph. Eur. and the applicable ICH/CHMP guidelines. Analytical procedures are suitable validated. Batch analyses have been performed on production scale batches for both strengths.
The batch analyses results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for finished product are adequately drawn up. All the results comply with the proposed specifications at all tested conditions in both types of packaging and no significant change in product quality was observed.
Based on presented data on production scale batches for both strengths packaged in blisters of cold formed OPA/Al/PE+desiccant film - aluminium/PE foil and HDPE container/ PP closures with desiccant insert, shelf life of 18 months when stored in the original packaging material in order to protect from moisture is acceptable.

III. NON-CLINICAL ASPECTS

Discussion on the non-clinical aspects
Pharmacodynamic, pharmacokinetic and toxicologic properties of esomeprazole are well known. As esomeprazol is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

No specific clinical studies, apart from the bioequivalence studies, have been provided as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

IV.2 Pharmacokinetics

To support the application, the applicant has submitted 3 bioequivalence studies:

- Single dose study with 40 mg gastro resistant capsules under fasting and fed conditions
- Single dose study with 20 mg gastro resistant capsules under fasting conditions
- Multiple dose study with 40 mg gastro resistant capsules under fasting conditions

The type of bioequivalence studies is in accordance with the CPMP Note for Guidance on Modified Release Oral and Transdermal Dosage Forms, for a delayed release formulation. All the conditions for biowaiver were fulfilled for the 20 mg and 40 mg strengths.

The pharmacokinetics of Esomeprazole are well established. Based on the available published literature including the brand leader's product information, a summary of pharmacokinetics is provided below.

Single dose study with 40 mg (fasting conditions)

Table 1. Pharmacokinetic parameters of **esomeprazole** (non-transformed values; arithmetic mean ± SD, t_{max} median, range):

N=18

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test					
Mean	2208.2	2220.9	1031.4	2.33	1.12
CV	68.8%	69.0%	53.0%	40.8%	32.3%
Reference					
Mean	2130.3	2140.7	962.6	2.08	1.09
CV	65.4%	65.5%	50.9%	24.7%	29.0
***Ratio (90% CI)**	94.89%-113.24%	94.96%-113.35%	97.90%-117.28%	-	-
Intra CV (%)	15.3%	15.3%	15.6%	-	-

**ln-transformed values*

Single dose study with 40 mg (fed conditions)

Table 2. Pharmacokinetic parameters of **esomeprazole** (non-transformed values; arithmetic mean ± SD, t_{max} median, range):

N=36

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test					
Mean	1587.0	1614.6	561.2	5.57	1.27
CV	75.8%	76.1%	72.3%	17.5%	37.6%
Reference					
Mean	1673.1	1685.5	611.8	4.28	1.13
CV	82.2%	82.4%	57.0%	25.8%	38.6%

***Ratio (90% CI)**	86.45%-104.07%	87.51%-104.86%	81.37%-103.41%	-	-
Intra CV (%)	23.6%	23.0%	30.8%	-	-

**ln-transformed values*

Single dose study with 20 mg (fasting conditions)

Table 3. Pharmacokinetic parameters of **esomeprazole** (non-transformed values; arithmetic mean ± SD, t_{max} median, range):

N=35

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test					
Mean	883.0	890.7	503.9	2.04	0.96
CV	58.5%	58.7%	35.0%	33.6%	39.3%
Reference					
Mean	894.5	902.1	531.7	1.49	0.97
CV	58.8%	58.8%	34.0%	34.1%	38.4%
***Ratio (90% CI)**	92.81%-104.79%	92.87%-104.77%	87.30%-103.08%	-	-
Intra CV (%)	15.1%	15.0%	20.8%	-	-

**ln-transformed values*

Multiple dose study with 40 mg (fasting conditions)

Table 4. Pharmacokinetic parameters of **esomeprazole** (non-transformed values; arithmetic mean ± SD, t_{max} median, range):

N=36

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test					
Mean	4032.5	4067.2	1593.0	1.92	1.48
CV	36.6%	37.1%	27.3%	27.2%	31.0%
Reference					
Mean	4096.6	4138.7	1453.3	1.73	1.48
CV	36.2%	36.6%	21.6%	34.5%	28.2%
***Ratio (90% CI)**	94.52%-102.51%	94.39%-102.32%	102.92%-116.73%	-	-
Intra CV (%)	10.2%	10.1%	15.9%	-	-

**ln-transformed values*

Based on these studies, the bioequivalence of the test product Esomeprazole 20 mg and 40 mg gastro-resistant capsules to the the reference product Nexium mups 20 mg and 40 mg gastro-resistant tablets is demonstrated after single-doses administration (20 mg and 40 mg) under fasting and fed conditions and after multiple-doses administration (40 mg) under fasting conditions.

IV.3 Pharmacodynamics

The application contains an adequate review of published clinical data. No new data are presented.

IV.4 Clinical efficacy

Esomeprazole has a well-recognised efficacy.

IV.5 Clinical safety

Esomeprazole has acceptable level of safety in the claimed indications and has been widely used in many countries.

IV.6 Discussion on the clinical aspects

Since the product refers and has been shown to be essentially similar to a product based on a full dossier with regard to clinical efficacy and safety data, no further data have been submitted or are considered necessary.

Pharmacovigilance Plan
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Minimisation Plan

The MAH has included a satisfactory justification for not submitting a Risk Management Plan for the product.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use and indicate that the PILs are well structured and organized, easy to understand and written in a comprehensive manner.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical documentation in relation to esomeprazole magnesium dihydrate and finished products are of sufficient quality in view of the present European regulatory requirements.
It can be concluded, that the proposed products are acceptable form the quality point of view.

Pharmacodynamic, pharmacokinetic and toxicological properties of esomeprazole are well known. As esomeprazole is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is thus appropriate and has been provided by the Applicant. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The SPC is in line with the innovator product Nexium 20mg and 40mg, gastro-resistant tablets.

The application contains an adequate review of published clinical data. The bioequivalence studies confirm that the test product (Esomeprazole 20 mg and 40 mg gastro-resistant capsules, hard) is bioequivalent to the Reference formulation (Nexium mups 20 mg and 40 mg gastro-resistent tablets) with respect to rate and extent of availability, and is well tolerated. The risk/benefit ratio is considered positive and Marketing Authorisation was granted in Slovenia in October 2009 and January 2010.

Module 6: Steps taken after the initial procedure with an influence on the Public Assessment Report – "Update"

Public Assessment Report

Update

Emozul 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0108/001-002/MR

Esmep 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0109/001-002/MR

Esmera 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0110/001-002/MR

Esomeprazol Hygia 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0111/001-002/MR

Esora 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0112/001-002/MR

Faras 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0113/001-002/MR

Peros 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0114/001-002/MR

Prazos 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0115/001-002/MR

Sempra 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0116/001-002/MR

Zaros 20 mg and 40 mg gastro-resistant capsules, hard
SI/H/0117/001-002/MR

Esomeprazole magnesium dihydrate

SI/H/0108-0117/001-002/MR

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)