SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Esomeprazole gastro-resistant hard capsules 20 mg
Esomeprazole gastro-resistant hard capsules 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg: Each gastro-resistant capsule contains 22,25 mg esomeprazole magnesium trihydrate equivalent to 20 mg esomeprazole.

40 mg: Each gastro-resistant capsule contains 44,5 mg esomeprazole magnesium trihydrate equivalent to 40 mg esomeprazole.

Excipients with known effect:
20 mg: Each capsule contains approximately 13.22 mg of sucrose and 0.02 micrograms benzoic acid (see section 4.4).
40 mg: Each capsule contains approximately 26.43 mg of sucrose and 0.04 micrograms benzoic acid (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule,
20 mg: Off white to pale brown coloured pellets filled in blue opaque hard gelatin capsules imprinted with “G” on cap and “59” on the body. The actual size of the capsule is length 13.5 – 15.0 mm x width 5.0 – 5.6 mm.

40 mg: Off white to pale brown coloured pellets filled in white opaque hard gelatin capsules imprinted with “G” on cap and “60” on the body. The actual size of the capsule is length 15.0 – 17.5 mm x width 5.5 – 6.1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Esomeprazole is indicated in adults 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 i.v. induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

Adolescents from the age of 12 years:
Gastro-esophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis.
- long-term management of patients with healed esophagitis to prevent relapse.
- symptomatic treatment of gastro-esophageal reflux disease (GERD).

In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori.*

4.2 Posology and method of administration

Posology

Adults

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. 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.

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 Esomeprazole 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 i.v. induced prevention of rebleeding of peptic ulcers.
40 mg once daily for 4 weeks after i.v. induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome
The recommended initial dosage is 40 mg Esomeprazole 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.

Special Populations

Renal impairment
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).

Hepatic impairment
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 Esomeprazole should not be exceeded (see section 5.2).

Elderly
Dose adjustment is not required in the elderly.

Paediatric population

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.

Treatment of duodenal ulcer caused by Helicobacter pylori
When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

The posology recommendation is:

Weight	**Posology**
30 - 40 kg	Combination with two antibiotics: Esomeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for one week.

> 40 kg	Combination with two antibiotics: Esomeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered together twice daily for one week.

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

Method of administration
The capsules should be swallowed whole with liquid. The capsules should not be chewed or crushed. For patients who have difficulty in swallowing, the capsules can be opened and their content dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. Stir and drink the liquid with the granules immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The granules must not be chewed or crushed.

For patients who cannot swallow, the content of the capsules can be dispersed 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. For preparation and administration instructions see section 6.6.

4.3 Contraindications

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

Esomeprazole should not be used concomitantly with nelfinavir or rilpivirine (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 esomeprazole may alleviate symptoms and delay diagnosis.

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

On demand treatment
Patients on on-demand treatment should be instructed to contact their physician if

their symptoms change in character.

Helicobacter pylori eradication
When prescribing esomeprazole for eradication of *Helicobacter pylori* possible drug 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 drugs metabolised via CYP3A4 such as cisapride.

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

Absorption of vitamin B12
Esomeprazole, 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.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture
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 esomeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicinal products

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.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

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.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms.

Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed.

Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

Sucrose

This medicinal product contains sucrose. Patients with rare hereditary problems of

fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Benzoic acid.
This medicine contains 0.02 micrograms of benzoic acid in each dosage unit containing 20 mg of esomeprazole.
This medicine contains 0.04 micrograms of benzoic acid in each dosage unit containing 40 mg of esomeprazole.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole 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

Effects of esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors
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.

Co-administration of omeprazole (40 mg qd) 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 %. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration of esomeprazole and nelfinavir is contraindicated (see section 4.3).

For atazanavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended (see section 4.4). 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 qd) 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 qd without omeprazole 20 mg qd.

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).

Rilpivirine:

Following multiple doses of rilpivirine (150 mg, daily) and omeprazole (20 mg, daily), AUC was decreased by 40%, Cmax by 40%, and Cmin by 33% for rilpivirine. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration of esomeprazole and rilpivirine is contraindicated (see section 4.3).

Methotrexate

When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Medicinal products with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other PPIs might increase or decrease the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 % (up to 30 % in two out of ten subjects). Digoxin toxicity has been rarely reported. However,

caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

Diazepam
Concomitant administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin
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.

Voriconazole
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15 % and 41 %, respectively.

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. 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.

Cisapride
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 ($t_{1/2}$) 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).

Warfarin
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.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40 % and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14 %.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40 % of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicinal products with no clinically relevant interaction
Amoxicillin and quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Naproxen or rofecoxib
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 medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4
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 CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUCτ 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.

Medicinal products which induce CYP2C19 and/or CYP3A4
Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole.
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/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Breastfeeding
It is not known whether esomeprazole is excreted in human breast milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breastfeeding.

Fertility
Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Esomeprazole has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported (see section 4.8). If affected patients should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

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).

System Organ Class	**Frequency**	**Undesirable Effect**
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
	Not known	Hypomagnesaemia (see section 4.4); severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Rare	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)

	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
	Not known	Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine (see section 4.4)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patient's renal failure has been reported concomitantly
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal products 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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

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: Drugs for acid-related disorders, 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.

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.

Pharmacodynamic effects
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.

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 drugs 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 haemostasis, 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 %.

During treatment with antisecretory medicinal products serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term treatment with antisecretory drugs 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* and, in hospitalised patients, possibly also *Clostridium difficile*.

Clinical efficacy

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.

Paediatric population
In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61 % of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

5.2 Pharmacokinetic properties

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

Distribution
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.

Biotransformation
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.

Elimination
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. 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 drug is found in urine.

Linearity/non-linearity

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.

Special patient populations

Poor metabolisers

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.

Gender

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.

Hepatic impairment

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.

Renal impairment
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.

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

Paediatric population
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 drug concentration (t_{max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
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

Capsule content
Glycerol monostearate
Hypromellose 2910
Magnesium stearate
Polysorbate 80
Talc
Triethyl citrate
Hydroxy propyl cellulose containing:
Hydroxypropyl cellulose

Silica, Colloidal Anhydrous
Sugar spheres containing:
Maize Starch
Sucrose

Methacrylic acid - ethyl acrylate copolymer (1:1) dispersion containing:
Methacrylic acid - ethyl acrylate copolymer (1:1)
Sodium Laurilsulfate
Simeticone
Polysorbate 80

Simeticone (emulsion) containing:
Simeticone
Polyoxyethylene Sorbitan Tristearate
Methylcellulose
Poly (ethylene oxide) stearate
Glyceryl stearate
Xanthan Gum
Benzoic Acid
Sorbic Acid
Sulfuric Acid

Capsule shell
Gelatin
Titanium dioxide (E171)
Sodium lauryl sulphate
Sorbitan Monolaurate
Brilliant Blue FCF – (only in 20 mg)

Printing Ink containing:
Shellac
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

For Blister Pack:
Do not store above 25°C. Store in the original package in order to protect from moisture.

For Bottle Pack:
This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Esomeprazole gastro-resistant hard capsules 20 mg, 40 mg is available in Alu-OPA/ALU/PVCblister pack containing 7, 14, 15, 28, 30, 56, 60, 90 and 98 capsules.

Esomeprazole gastro-resistant hard capsules 20 mg, 40 mg is available in HDPE bottle with polypropylene child-resistant closure pack containing 28, 30 and multipacks containing 90 (3 bottle packs of 30's count (3x30) in one carton) capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Administration through Nasogastric tube (NG tube)
The suspension can be given only through a nasogastric tube size 8 Fr or larger.

1. Open the capsule and empty the granules into a 60 mL catheter tipped syringe.
2. Mix with 50 mL of drinking water.
3. Use only a catheter tipped syringe to give esomeprazole magnesium delayed-release capsules through a NG tube.
4. Replace the plunger and shake the syringe well for 15 seconds.
5. Hold the syringe with the tip up and check for any granules remaining in the tip.
6. Do not give the granules if they have dissolved or have broken into pieces.
7. Attach the syringe to the NG tube. Give the medicine right away in the syringe through the NG tube into the stomach.
8. After giving the granules, fill the syringe with 20 ml of water and repeat step 5 if necessary to wash down any sediment left in the syringe to flush the NG tube.

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

7. MARKETING AUTHORISATION HOLDER

PharmConsul s.r.o.

Krcmarovska 223/33

Miskovice

Prague

19600

Czechia

8. MARKETING AUTHORISATION NUMBER(S)

MA114700301-2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th May 2026

10. DATE OF REVISION OF THE TEXT

May 2026