1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ZOEGAS® 40 mg, Gastro-resistants microgranules in capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Esomeprazole magnesium dihydrate	43,37 mg
(Equivalent to Esomeprazole	40 mg)

Excipients

Sugar spheres (1)	17,48 mg
Hypromellose 3cP	39,90 mg
Dimethicone emulsion 35% (2)	0,73 mg
Polysorbate 80	4,38 mg
Mannitol	34,53 mg
Diacetylated monoglycerides	1,53 mg
Talc	2,06 mg
Methacrylic acid-ethyl acrylate copolymer dispersion 30% (1:1) (3)	25,90 mg
Triethyl citrate	2,59 mg
Stearoyl macroglycerides	2,59 mg
Purified water	does not appear in the finished product

For one capsule

For a full list of excipients, see section 6.1.

Excipients with known effect: sucrose, propyl-p-hydroxybenzoate, methyl-p-hydroxybenzoate

3. PHARMACEUTICAL FORM

Gastro-resistants microgranules in capsules.

ZOEGAS® 40 mg is size 3 capsule with opaque yellow cap and body containing off-white to greyish spherical microgranules

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The capsules of ZOEGAS 40mg are indicated in adults for:

- Gastroesophageal Reflux (GER) : treatment of erosive reflux esophagitis
- Treatment of Zollinger Ellison Syndrome.
- Prolonged treatment after I.V. induced prevention of rebleeding of gastric-duodenal ulcers.

4.2. Posology and method of administration

Posology

Adults

- **Gastroesophageal Reflux (GER)**

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.

- **Treatment of Zollinger-Ellison Syndrome**

The recommended initial dosage is ZOEGAS 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 are

controlled on doses between 80 to 160 mg of esomeprazole daily. With doses above 80 mg daily, the daily dose should be divided and given twice 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.

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 of ZOEGAS 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 (GER)

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.

Children below the age of 12 years

ZOEGAS should not be used in children under 12 years in the absence of available data.

4.3. Method of administration

The capsules should be swallowed whole with liquid. They should not be chewed or crushed.

For patients who have difficulty in swallowing:

1) The capsules may be opened and their contents (microgranules) dispersed in half a glass of non-gaseous water. No other liquids should be used.
2) Stir to disintegrate and drink immediately the liquid with the pellets or within 30 minutes. Always stir the mixture before swallowing it.
3) 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 content of the capsules can be dispersed in non- gaseous 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 hereafter:

1. Put the content of one capsule in approximately 25 ml or 50 ml of water. (For some tubes, 50 ml volume of water is needed to disperse the granules and prevent the obstruction of the tube). Stir.
2. Take the suspension into a syringe and add approximately 5 ml of air.
3. Immediately shake the syringe for approximately 2 minutes to disperse the pellets.
4. Hold the syringe with the tip up and check that the tip has not clogged.

5. Attach the syringe to the tube whilst maintaining the above position.

6. Shake the syringe and position it with the tip pointing down. Immediately inject 5–10 ml into the tube. Invert the syringe tip pointing up and shake (the syringe must be held with the tip pointing up to avoid clogging of the tip).

7. 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.

8. Fill the syringe with 25 ml of water and 5 ml of air and repeat step 6 if necessary, to wash down any sediment left in the syringe. For some tubes, 50 ml of water is needed.

4.4. Contraindications

Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients listed in section 6.2.

Esomeprazole should not be used concomitantly with nelfinavir (see section 4.6).

4.5. Special warnings and precautions for use

In the presence of any of these alarm symptoms (e.g. important unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, the possibility of a malignant lesion should be excluded because the use of ZOEGAS 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 therapy should be considered.

Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when an eradiation treatment is taken concomitantly with other drugs metabolised via CYP3A4 such as cisapride.

Gastrointestinal infections

Treatment with IPP may lead to slightly increased risk of gastrointestinal infections caused by germs such as Salmonella and Campylobacter (see section 6.1).

Absorption of vitamin B12

Esomeprazole, as all gastric acids secretion-decreasing 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 cases had 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 also begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium supplementation and discontinuation of the PPI.

For patients requiring a prolonged treatment or in case of association of PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and regularly 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 recommendations and they should receive an adequate intake of vitamin D and calcium.

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 risk of 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 impact on interactions with other drugs, due to fluctuating plasma concentrations of esomeprazole should be considered. See section 4.5.

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 temporarily for 5 days before CgA measurements (see section 6.1).

Sucrose

This medicine contains sucrose. Its use is not recommended in patients with fructose intolerance, glucose-galactose malabsorption syndrome or sucrase/isomaltase deficiency.

Parahydroxybenzoates

This medicine contains parahydroxybenzoates and may cause allergic reactions (possibly delayed).

4.6. 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 interactions are not always known. Increased gastric pH observed during omeprazole treatment may change the absorption of the protease inhibitors. There are other mechanisms of interactions that occur via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased plasma concentrations have been reported when given together with omeprazole; concomitant administration of omeprazole and these medicines is therefore not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg associated with ritonavir 100 mg to healthy volunteers resulted in a significant decrease in atazanavir plasma concentrations (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the effect of omeprazole on atazanavir plasma concentrations.

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 administered alone. 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%.

Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section 4.5) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section 4.4).

For saquinavir (with concomitant ritonavir), increased plasma concentrations (80-100%) have been reported during association with omeprazole (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (associated to ritonavir) and amprenavir (associated to ritonavir).

Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir (associated or not to ritonavir). Treatment with omeprazole 40 mg once daily had no effect on the exposure of lopinavir (associated with ritonavir).

Methotrexate

When administrated together with PPIs, increase on methotrexate concentrations have been observed in some patients. In high-dose methotrexate administration a temporary discontinuation of esomeprazole treatment may need to be considered.

Tacrolimus

Concomitant administration of tacrolimus and esomeprazole has been reported to increase the plasma concentrations 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 secretion inhibition during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of certain medicinal products such as ketoconazole, itraconazole and erlotinib can decrease while the absorption of medicinal products such as 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. Monitoring of treatment by 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 of esomeprazole resulted in a 45% decrease in diazepam clearance, metabolized by CYP2C19.

Phenytoin

Concomitant administration of 40 mg of esomeprazole resulted in a 13% increase in plasma concentrations 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 plasma concentrations of voriconazole (a CYP2C19 substrate) and C_{max} and AUC_{τ} increasing by 15% and 41%, respectively.

Cilostazol

Esomeprazole as well as omeprazole 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 of esomeprazole resulted in a 32% increase in area under the plasma concentration 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 4.5).

Warfarin

Concomitant administration of 40 mg of 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 daily via oral route) 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 esomeprazole and 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 twice a day), resulted in a doubling of the air under curve (AUC) of esomeprazole.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole C_{max} and AUC.

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.

4.7. Fertility, pregnancy and lactation

Pregnancy

Clinical data on exposed pregnancies with ZOEGAS 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/foetal development.

Animal studies with the racemic mixture do not indicate direct or indirect deleterious effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing ZOEGAS to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity effects of esomeprazole.

Animal studies do not indicate direct or indirect deleterious effects with respect to reproduction (see section 5.3).

Breast-feeding

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 breast-feeding.

Fertility

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

4.8. 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 5.8). Affected patients should not drive or use machines.

4.9. 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 reported or suspected in the clinical trials of esomeprazole and post-marketing. None was found to be dose-depended. The undesirable effects 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 4.5); 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
	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 severe liver insufficiency
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 and systemic disorders	Uncommon	Fracture of the hip, wrist or spine (see section 4.5)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patients renal failure has been reported concomitantly.
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site anomalies	Rare	Malaise, increased sweating

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.10. Overdose

There is very limited experience to date with deliberate overdose. The symptoms described when taking 280 mg were gastrointestinal symptoms and weakness signs.

Single doses of 80 mg daily were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. In case of overdose, treatment should be symptomatic and aim to preserve vital functions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors

ATC Code: A02BC05

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*-isomers 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), the basal acid secretion and the stimulated acid secretion.

Pharmacodynamic effects

After oral dosing with esomeprazole 20 mg and 40 mg, the anti-secretory 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 GER 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 parameter reflecting plasma concentration, a relationship between inhibition of acid secretion and AUC 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 twice daily 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 either 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 on open posology 40 mg oral esomeprazole for 27 days for acid secretion decrease. The occurrence of rebleeding frequency 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 was 7.7% vs 13.6%.

During treatment with antisecretory medicinal products, serum gastrin concentration increases in response to the decreased gastric acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. The literature data indicates that treatment with a proton pump inhibitor should be discontinued at least 5 days prior to the measurement of the CgA level. If CgA and gastrin levels are not standardized within 5 days, measurements should be repeated 14 days after discontinuation of esomeprazole therapy.

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

During long-term treatment with antisecretory drugs, cases of gastric glandular cysts have been reported to slightly increase. 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-intestinal 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 NSAIs, including COX-2 selective NSAIDs.

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

Paediatric population

In a study in paediatric GER 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 instable in acid medium. It is administered orally as gastro-resistant 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 anti-secretary effect of esomeprazole.

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 (CYP).

The major part of the metabolism of esomeprazole is dependent on the polymorphic enzyme CYP2C19, responsible for the formation of the hydroxy- and demethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoenzyme, CYP3A4, responsible for the formation of esomeprazole sulphone, the main plasmatic metabolite.

Elimination

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme or 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 two 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 administrated 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 twice per day. 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.

Specific 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 of area under curve (AUC) of the plasma concentration 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 curve of the plasma concentration is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration of esoomeprazole. 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 and 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 of esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (t_{max}) in 12 to 18 year-olds children are similar to that in adults for both esomeprazole doses.

5.3. Preclinical safety data

Non-clinical data reveal no special risk for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic risk, 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 tumors. These gastric changes in the rat are the result of sustained, pronounced hypergastrinaemia secondary to

reduced secretion of gastric acid and are observed after long-term treatment in this animal with inhibitors of acid secretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres (1)
Hypromellose 3Cp
Dimethicone emulsion 35% (2)
Polysorbate 80
Mannitol Diacetylated monoglycerides
Talc
Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30% (3)
Triethyl citrate
Stearoyl macroglycerides
Water purified

(1) Sucrose and maize starch

(2) Propyl parahydroxybenzoate (E216), methyl parahydroxybenzoate (E218), ascorbic acid, sodium benzoate, sorbitan propylene glycol monolaurate, octylphenoxy-Polyethoxy-ethanol, purified water and propylene glycol.

(3) Methacrylic acid and ethyl acrylate copolymer, purified water, sodium laurilsulfate and polysorbate 80.

Capsule composition: Gelatin, Yellow iron oxide (E 172), Titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package away from moisture.

6.5 Nature and contents of container

Gastro-resistant microgranules in capsules packed in Alu-Alu blister. Available in box of 7, 14 & 28.
Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with current regulations.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

- **Name and address of the Headquarter of the marketing authorization holder:**

COOPER PHARMA
41, Rue Mohamed DIOURI, 20110 Casablanca
Morocco

- **Manufacturing site address:**

→ **Manufacturing of gastro-resistant microgranules:**

ETHYPHARM
Z.I. de Saint Arnoult
28170 Châteauneuf en Thymerais
France

→ **Capsules filling / Control / Packaging & Batch release**

COOPER PHARMA
Route 107, Km 2,5 Douar Oulad Sidi Abbou - Tit Melil
Casablanca - Morocco

8. MARKETING AUTHORISATION NUMBER(S)

20/4364/DGC/PHS/2018

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 06 Jun 2018
Date of last renewal: Not applicable

10. DATE OF REVISION OF THE TEXT

12/2018

PRESCRIPTION AND DELIVERY CONDITIONS

Table C (List II)