

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Esomeprazole Orifarm 10 mg granules for gastro-resistant oral suspension in sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains: 10 mg esomeprazole (as esomeprazole magnesium).

Excipients with known effect: Each sachet contains 4 mg sucrose and 3 g glucose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for gastro-resistant oral suspension in sachet.

A mix of light yellow and off-white to cream colored fine granules. The oral suspension is a thick light yellow liquid containing suspended pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Esomeprazole Orifarm is primarily indicated for:

Paediatric population

Children 1-11 years old

Gastroesophageal Reflux Disease (GERD)

- treatment of endoscopically proven erosive reflux esophagitis
- symptomatic treatment of gastroesophageal reflux disease (GERD)

Children over 4 years of age

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

Adults and adolescents from the age of 12 years

For indications in patients from the age of 12 years reference is made to gastro-resistant tablets containing esomeprazole.

Esomeprazole Orifarm may also be used by patients having difficulty swallowing dispersed gastro-resistant tablets containing esomeprazole.

4.2 Posology and method of administration

Posology

Paediatric population

Children 1–11 years with a bodyweight of ≥ 10 kg

Gastroesophageal Reflux Disease (GERD)

- Treatment of endoscopically proven erosive reflux esophagitis
 - Weight ≥ 10 - < 20 kg: 10 mg once daily for 8 weeks.
 - Weight ≥ 20 kg: 10 mg or 20 mg once daily for 8 weeks.
- Symptomatic treatment of gastroesophageal reflux disease (GERD)
 - 10 mg once daily for up to 8 weeks.

Doses over 1 mg/kg/day have not been studied.

Children over 4 years of age

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 kg	Combination with 2 antibiotics: Esomeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for 1 week.
30 - 40 kg	Combination with 2 antibiotics: Esomeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for 1 week.
> 40 kg	Combination with 2 antibiotics: Esomeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered together twice daily for 1 week.

Children below the age of 1 year

The experience of treatment with esomeprazole in infants < 1 year is limited and treatment is therefore not recommended (see section 5.1).

Adults and adolescent from the age of 12 years

For posology in patients from the age of 12 years reference is made to esomeprazole gastro-resistant tablet SmPCs.

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 ≥ 12 years with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded. For children 1-11 years with severe liver impairment, a maximum dose of 10 mg should not be exceeded (see section 5.2).

Elderly

Dose adjustment is not required in the elderly.

Method of administration

For a 10 mg dose empty the contents of a 10 mg sachet into a glass containing 15 ml water. For a 20 mg dose empty the contents of two 10 mg sachets into a glass containing 30 ml water. Do not use

carbonated water. Stir the contents until the granulate has been dispersed and leave for a few minutes to thicken. Stir again and drink within 30 minutes. The granules must not be chewed or crushed. Rinse with 15 ml water to obtain all granules.

For patients who have a nasogastric or gastric tube in place: see section 6.6 for preparation and administration instructions.

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 (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. Long-term treatment is indicated in adults and adolescents (12 years and older, see section 4.1).

On demand treatment

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. On demand treatment has not been investigated in children and is therefore not recommended in this patient group.

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 triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4, such as cisapride.

Gastrointestinal infections

Treatment with proton pump inhibitors (PPIs) may lead to a 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 PPIs like esomeprazole for at least 3 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 medicinal products that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fractures

PPIs, 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 recognized risk factors. Observational studies suggest that PPIs 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)

PPIs 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 PPIs may increase the risk of SCLE with other PPIs.

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 PPIs 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 medicinal products metabolized 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), 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 and glucose

This medicinal product contains sucrose and glucose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumors. 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 PPIs treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of esomeprazole on the pharmacokinetics of other medicinal products

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 CYP2C19.

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 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. 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 with esomeprazole and atazanavir is not recommended (see section 4.4) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section 4.3).

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).

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 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 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 2 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 metabolizing enzyme. Thus, when esomeprazole is combined with medicinal products metabolized by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal

products 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 and cisapride 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 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 metabolized 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 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. Long-term treatment is indicated in adults and adolescents (12 years and older, see section 4.1).

Medicinal products which induce CYP2C19 and/or CYP3A4

Medicinal products 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

Clinical data on exposed pregnancies with esomeprazole 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.

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

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3)

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 and 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, diarrhea 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 program for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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, diarrhea, 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),

		drug reaction with eosinophilia and systemic symptoms (DRESS)
	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 patients 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 utilized.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitor, 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-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 1 hour. After repeated administration with 20 mg esomeprazole once daily for 5 days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6 – 7 hours after dosing on day 5.

After 5 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 4 weeks, and in 93% after 8 weeks.

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 (PPIs) 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 medicinal products 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 PPIs, increases gastric count of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalized patients, possibly also *Clostridium difficile*.

Paediatric population

GERD – 1-11 years of age

In a multicenter, parallel-group study, 109 paediatric patients with endoscopically proven GERD (1 to 11 years of age) were treated with esomeprazole once daily for up to 8 weeks to evaluate safety and tolerability. Dosing by patient weight was as follows:

- Weight <20 kg: once daily treatment with esomeprazole 5 mg or 10 mg.
- Weight ≥20 kg: once daily treatment with esomeprazole 10 mg or 20 mg.

Patients were endoscopically characterized as to the presence or absence of erosive esophagitis. Fiftythree patients had erosive esophagitis at baseline. Of the 45 patients who had follow-up endoscopy, 42 (93.3%) of these patients had their erosive esophagitis resolved (88.9%) or improved (4.4%) after 8 weeks of treatment.

GERD – 0 to 11 months of age

In a placebo-controlled study (98 patients aged 1-11 months) efficacy and safety in patients with signs and symptoms of GERD were evaluated. Esomeprazole 1 mg/kg once daily was given for 2 weeks (open-label phase) and 80 patients were included for an additional 4 weeks (double blind, treatmentwithdrawal phase). There was no significant difference between esomeprazole and placebo for the primary endpoint time to discontinuation due to symptom worsening.

In a placebo-controlled study (52 patients aged <1 month) efficacy and safety in patients with symptoms of GERD were evaluated. Esomeprazole 0.5 mg/kg once daily was given for a minimum of 10 days. There was no significant difference between esomeprazole and placebo in the primary endpoint, change from baseline of number of occurrences of symptoms of GERD.

Results from the paediatric studies further show that 0.5 mg/kg and 1.0 mg/kg esomeprazole in <1 month old and 1 to 11 month old infants, respectively, reduced the mean percentage of time with intra-oesophageal pH<4.

The safety profile appeared to be similar to that seen in adults.

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 tumors.

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 metabolized 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 metabolizers.

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 $2.9 \pm 1.5\%$ of the population lack a functional CYP2C19 enzyme and are called poor metabolizers. In these individuals the metabolism of esomeprazole is probably mainly catalyzed 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 metabolizers than in

subjects having a functional CYP2C19 enzyme (extensive metabolizers). 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 in adolescents 12-18 years of age, the total exposure (AUC) and the time to reach maximum plasma drug concentration ($t_{\max}$) was similar to that in adults.

Children 1 – 11 years:

Following repeated dose administration of 10 mg esomeprazole, the total exposure (AUC) was similar within the age range 1 to 11 years and the exposure was similar to the exposure seen with the 20 mg dose in adolescents and adults.

Following repeated dose administration of 20 mg esomeprazole, the total exposure (AUC) was higher in 6 to 11 year-olds compared to the same dose in adolescents and adults.

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. No new or unexpected toxicity findings were observed in juvenile rats and dogs, after administration of esomeprazole for up to 3 months, as compared to the adult animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Esomeprazole granules:

Sugar spheres
Ethylcellulose
Magnesium stearate
Povidone
Magnesium oxide
Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion
Triethyl citrate
Glycerol monostearate
Polysorbate 80
Talc

Excipient granules:

Glucose monohydrate
Xanthan gum
Crospovidone
Iron oxide, yellow (E172)
Hydroxypropylcellulose
Citric acid monohydrate (for pH adjustment)
Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

To be used within 30 minutes after reconstitution.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Sachets (containing granules): Laminate consisting of 3 layers: polyethylene terephthalate (PET), aluminium and low density polyethylene (LDPE).

Carton containing 28, 30, 32, 35, 37, 50 or 56 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

For patients who have a nasogastric or gastric tube in place

1. For a 10 mg dose, add the contents of a 10 mg sachet into 15 ml of water
2. For a 20 mg dose add the contents of two 10 mg sachets into 30 ml of water
3. Stir

4. Leave for a few minutes to thicken
5. Stir again
6. Draw the suspension into a syringe
7. Inject through the enteric tube, French size 6 or larger, into the stomach within 30 minutes after reconstitution
8. Refill the syringe with 15 ml water for a 10 mg dose and 30 ml for a 20 mg dose
9. Shake and flush any remaining contents from the enteric tube into the stomach

Any unused suspension should be discarded.

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

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

2025-12-11