Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Esose 40mg

2. Qualitative and quantitative composition

Each vial contains Esomeprazole Sodium for injection

Eq. to Esomeprazole 40 mg

3. Pharmaceutical form

Powder for injection

White to off-white porous and uniform lyophilized powder.

4. Clinical particulars

4.1 Therapeutic indications

Esomeprazole Sodium for Injection 40 mg is indicated in adults for:

- gastric antisecretory treatment when the oral route is not possible, such as:
- gastroesophageal reflux disease (GERD) in patients with oesophagitis and/or severe symptoms of reflux
- healing of gastric ulcers associated with NSAID therapy
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
- prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Esomeprazole Sodium for Injection 40 mg is indicated in children and adolescents aged 1-18 years for:

- gastric antisecretory treatment when the oral route is not possible, such as:
- gastroesophageal reflux disease (GERD) in patients with erosive reflux esophagitis and/or severe symptoms of reflux.

4.2 Posology and method of administration

Adults

Gastric antisecretory treatment when the oral route is not possible

Patients who cannot take oral medication may be treated parenterally with 20– 40 mg once daily. Patients with reflux oesophagitis should be treated with 40 mg once daily. Patients treated symptomatically for reflux disease should be treated with 20 mg once daily.

For healing of gastric ulcers associated with NSAID therapy the usual dose is 20 mg once daily. For prevention of gastric and duodenal ulcers associated with NSAID therapy, patients at risk should be treated with 20 mg once daily.

Usually the intravenous treatment duration is short and transfer to oral treatment should be made as soon as possible.

Method of administration

For instructions on reconstitution of the medicinal product before administration,

Injection

40mg dose

5 ml of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes.

20 mg dose

2.5 ml or half of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.

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.

Patients with impaired hepatic function

GERD: Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg Esomeprazole should not be exceeded.

Elderly

Dose adjustment is not required in the elderly.

Paediatric population

Posology

Children and adolescents aged 1-18 years

Gastric antisecretory treatment when the oral route is not possible

Patients who cannot take oral medication may be treated parenterally once daily, as a part of a full treatment period for GERD (see doses in table below).

Usually the intravenous treatment duration should be short and transfer to oral treatment should be made as soon as possible.

Recommended intravenous doses of esomeprazole

Age group	Treatment of erosive reflux esophagitis	**Symptomatic treatment of GERD**
1-11 Years	Weight <20 kg: 10 mg once daily Weight ≥ 20 kg: 10 mg or 20 mg once daily	10 mg once daily
12-18 Years	40 mg once daily	20 mg once daily

Method of administration

For instructions on reconstitution of the medicinal product before administration.

Injection

40mg dose

5 ml of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes.

20 mg dose

2.5 ml or half of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.

10 mg dose

1.25 ml of the reconstituted solution (8 mg/ml) should be given as an intravenous injection over a period of at least 3 minutes. Any unused solution should be discarded.

4.3 Contraindications

Hypersensitivity to the active substance or to other substituted benzimidazoles.
Esomeprazole should not be used concomitantly with nelfinavir.

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.

Gastrointestinal infections

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

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 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 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 medicines

Co-administration of esomeprazole with atazanavir is not recommended. 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. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

Serious cutaneous adverse reactions (SCARs)

Serious 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, 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.

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. If CgA and gastrin levels have not returned to reference range after initial measurement

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 similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.
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 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 medicinal product 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 medicinal products metabolised 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. No *in vivo* interaction studies have been performed with the high dose intravenous regimen (80 mg + 8 mg/h). The effect of esomeprazole on medicinal products metabolised by CYP2C19 may be more pronounced during this regimen, and patients should be monitored closely for adverse effects during the 3-day intravenous treatment period.

Diazepam

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

Phenytoin

Concomitant oral administration of 40 mg esomeprazole and phenytoin 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 oral 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.

Warfarin

Concomitant oral 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 of oral esomeprazole, 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 coumarin 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 or 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 oral 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.

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 Pregnancy and Lactation

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 esomeprazole to pregnant women.
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicated no malformative or foeto/neonatal toxicity of esomeprazole.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity

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 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 (uncommon) have been reported. If affected patients should not drive or use machines.

4.8 Undesirable effects

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 medicinal product reactions have been identified or suspected in the clinical trials program for esomeprazole administered orally or intravenously and post-marketing when administered orally.
The reactions are classified according to frequency (very common ≥ 1/10, common ≥ 1/100, <1/10; uncommon ≥ 1/1000, <1/100; rare ≥ 1/10,000, <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 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

Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours).

Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole (the racemate) intravenous injection, especially at high doses, but no causal relationship has been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Paediatric population

A randomized, open-label, multi-national study was conducted to evaluate the pharmacokinetics of repeated intravenous doses for 4 days of once daily esomeprazole in paediatric patients 0 to 18 years old. A total of 57 patients

(8 children in the age group 1-5 years) were included for safety evaluation. The safety results are consistent with the known safety profile of esomeprazole, and no new safety signals were identified

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280 mg were gastrointestinal symptoms and weakness. Single oral doses of 80 mg esomeprazole and intravenous doses of 308 mg esomeprazole over 24 hours 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 inhibitor, 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 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 effect is similar irrespective of whether esomeprazole is administered orally or intravenously.

Using AUC as a surrogate parameter for plasma concentration, a

relationship between inhibition of acid secretion and exposure has been shown after oral administration of esomeprazole.

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 orally administered esomeprazole. The findings are considered to be of no clinical significance.

During long-term oral 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 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*.

Paediatric population

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 orally for 2 weeks (open- label phase) and 80 patients were included for an additional 4 weeks (doubleblind, treatment-withdrawal 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 orally 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 tumours.

5.2 Pharmacokinetic properties

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.

Biotranformation

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

Total exposure (AUC) increases with repeated administration of esomeprazole. This increase is dose- dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Following repeated doses of 40 mg administered as intravenous injections, the mean peak plasma concentration is approx. 13.6 micromol/l. The mean peak plasma concentration after corresponding oral doses is approx. 4.6 micromol/l. A smaller increase (of approx. 30%) can be seen in total exposure after intravenous administration compared to oral administration.

Special patient populations

Poor metabolisers

Approximately 2.9 ± 1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals, the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once daily administration of 40 mg oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolisers than in subjects with a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the posology of esomeprazole.

Gender

Following a single oral dose of 40 mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference

is seen after repeated once daily administration. Similar differences have been observed for intravenous administration of esomeprazole. 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 total exposure of esomeprazole. Therefore, a maximum dose of 20 mg should not be exceeded in GERD patients with severe dysfunction.

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

In a randomized, open-label, multi-national, repeated dose study, esomeprazole was given as a once-daily 3- minute injection over four days. The study included a total of 59 paediatric patients 0 to 18 years old of which 50 patients (7 children in the age group 1 to 5 years) completed the study and were evaluated for the pharmacokinetics of esomeprazole.

The table below describes the systemic exposure to esomeprazole following the intravenous administration as a 3- minute injection in paediatric patients and adult healthy subjects. The values in the table are geometric means (range). The 20 mg dose for adults was given as a 30-minute infusion. The $C_{ss,\ max}$ was measured 5 minutes post-dose in all paediatric groups and 7 minutes post-dose in adults on the 40 mg dose, and after stop of infusion in adults on the 20 mg dose.

Age group	Dose group	AUC (µ mol*h/l)	$C_{ss,max}$ (µ mol/l)
0-1 month*	0.5 mg/kg (n=6)	7.5 (4.5-20.5)	3.7 (2.7-5.8)
1-11 months*	1.0 mg/kg (n=6)	10.5 (4.5-22.2)	8.7 (4.5-14.0)
1-5 years	10 mg (n=7)	7.9 (2.9-16.6)	9.4 (4.4-17.2)
6-11 years	10 mg (n=8)	6.9 (3.5-10.9)	5.6 (3.1-13.2)
	20 mg (n=8)	14.4 (7.2-42.3)	8.8 (3.4-29.4)
	20 mg (n=6)**	10.1 (7.2-13.7)	8.1 (3.4-29.4)
12-17 years	20 mg (n=6)	8.1 (4.7-15.9)	7.1 (4.8-9.0)
	40 mg (n=8)	17.6 (13.1-19.8)	10.5 (7.8-14.2)
Adults	20 mg (n=22)	5.1 (1.5-11.8)	3.9 (1.5-6.7)
	40 mg (n=41)	12.6 (4.8-21.7)	8.5 (5.4-17.9)

* A patient in the age group 0 up to 1 month was defined as a patient with a corrected age of ≥ 32 complete weeks and
< 44 complete weeks, where corrected age was the sum of the gestational age and the age after birth in complete weeks. A patient in the age group 1 to 11 months had a corrected age of ≥ 44 complete weeks.

** Two patients excluded, 1 most likely a CYP2C19 poor metabolizer and 1 on concomitant treatment with a CYP3A4 inhibitor

Model based predictions indicate that $C_{ss,max}$ following intravenous administration of esomeprazole as a 10-minute, 20-minute and 30-minute infusions will be reduced by on average 37% to 49%, 54% to 66% and 61% to 72%, respectively, across all age and dose groups compared to when the dose is administered as a 3- minute injection.

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:

Oral carcinogenicity studies in the rat with the racemic mixture have

shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects 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. In the non-clinical program for esomeprazole intravenous formulation there was no evidence of vaso-irritation but a slight tissue inflammatory reaction at the injection site after subcutaneous (paravenous) injection.

6. Pharmaceutical Particulars

6.1 List of Excipients

There are no Excipients added in the product

6.2 Incompatibilities

This medicinal product must not be used with other medicinal products.

6.3 Shelf-Life

24 Months

6.4 Special Precautions for storage

Store below 30° C. Store in the original package in order to protect from light.

6.5 Nature and Content of container

7.5 mL Clear Molded Glass Vial USP Type-III Containing Sterile Esomeprazole Sodium 40 mg.

7. Marketing Authorization Holder

TAWWAB PHARMA PVT. LTD.
Sudarshan Sky Garden, D Block 1201, GB Road, Thane-400615, India. Email: Info@tawwabpharma.com
Telephone no. 00919769386568

8. Marketing Authorization Number

CTD10771

9. Date of first authorization/renewal of the authorization

26/04/2017

10. Date of revision of the text

10/05/2025