SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT
ESSİUM 40 mg Powder For Solution For I.V. Injection/Infusion

2.QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Substance:
Each vial contains 42,5 mg esomeprazole sodium equivalent to 40 mg esomeprazole.

Excipients:

Disodium edetate dehydrate	1.50 mg
Sodium hydroxide	q.s. pH 9.0– 11.0

For a full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM
Powder for solution for injection and infusion.
White to light yellow colored lyophilized powder.

4.CLINICAL PARTICULARS
4.1 Therapeutic indications

- ESSİUM injection and infusion is indicated in patients with following conditions, as an alternative to oral therapy when oral treatment is not appropriate:

Adults:
  - Gastroesophageal reflux disease in patients with esophagitis 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.
- Short-term maintenance of hemostasis and prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Children and adolescents aged 1-18 years
- gastric antisecretory treatment when the oral route is not possible, such as:
  - gastroesophageal reflux disease (GORD) in patients with erosive reflux esophagitis and/or severe symptoms of reflux.

4.2 Posology and method of administration

Posology / frequency and duration of administration
Adults:
Gastric antisecretory treatment when the oral route is not possible
Patients who cannot take oral medication may be treated parenterally with ESSİUM 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.

Prevention of rebleeding of gastric and duodenal ulcers
Following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers, 80 mg should be administered as a bolus infusion over 30 minutes, followed by a continuous intravenous infusion of 8 mg/h given over 3 days (72 hours).

The parenteral treatment period should be followed by oral acid-suppression therapy with 40 mg esomeprazole tablet once daily for 4 weeks.

Method of administration:
For preparation of reconstituted solution, see section 6.6.

Injection
40 mg 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 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.

Infusion
40 mg dose
The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

20 mg dose
Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Any unused solution should be discarded.

80 mg bolus dose
The reconstituted solution should be given as a continuous intravenous infusion over 30 minutes.

8 mg /h dose
The reconstituted solution should be given as a continuous intravenous infusion over a period of 71.5 hours (calculated rate of infusion of 8 mg/h).

Additional information on special populations
Renal failure:
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 failure:
GORD: 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 should not be exceeded.

Bleeding ulcers: Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, following an initial bolus dose of 80 mg bolus ESSİIUM for infusion, a continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient. (See Section 5.2)

Pediatric population:
Posology / frequency and duration of administration:

Children and adolescents aged 1-18 years:
Gastric anti-secretory 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 GORD (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 erosive reflux oesophagitis	Symptomatic treatment of GORD
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 application:
For preparation of reconstituted solution, see section 6.6.

Injection
40 mg 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.

Infusion
40 mg dose
The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

20 mg dose
Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Any unused solution should be discarded.

10 mg dose
A quarter of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Any unused solution should be discarded.

Geriatric population:
Dose adjustment is not required in the elderly.

4.3 Contraindications
Hypersensitivity to the active substance esomeprazole or to other substituted benzimidazoles or to any of the excipients used in the formulation.

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. Treatment with ESSİUM may alleviate symptoms and delay diagnosis.

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

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

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.

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

Bone fracture:
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hypomagnesemia:
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on

prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 5 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

A pharmacokinetic/pharmacodynamic interaction is observed between clopidogrel (300 mg loading dose / 75 mg maintenance dose) and esomeprazole (oral 40 mg daily). This resulted in an average 40% reduction in exposure to the active metabolite of clopidogrel and in a maximum inhibition (including ADP) of platelet aggregation with a mean reduction of 14%. Based on this data, concomitant use of esomeprazole and clopidogrel should be avoided (see Section 4.5).

Sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per ml, i.e it is essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction
Drug interaction studies have been performed only in adults.

Effect of esomeprazole on the pharmacokinetics of other drugs:
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).

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Co-administration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. This interaction is unlikely to be of clinical relevance. Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients, dose adjustment was not needed in this study.

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

A pharmacokinetic/pharmacodynamic interaction is observed between clopidogrel (300 mg loading dose / 75 mg maintenance dose) and esomeprazole (oral 40 mg daily). This resulted in an average 40% reduction in exposure to the active metabolite of clopidogrel and in a maximum inhibition (including ADP) of platelet aggregation with a mean reduction of 14%.

The results of several observational studies are inconsistent with respect to increased risk, or there is no increase in the risk of CV thromboembolic events when clopidogrel is used in combination with PPI.

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 metabolites 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.

Both omeprazole and esomeprazole act as an inhibitor of CYP 2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26% and one of its active metabolites by 29% and 69%, respectively.

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.

When given together with proton pump inhibitors, 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.

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 once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, C_{max} and C_{min} and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%.

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole. Concomitant administration with esomeprazole and drugs such as atazanavir and nelfinavir is not recommended due to similar pharmacokinetic effects and pharmacodynamic properties of omeprazole with esomeprazole.

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

Effects of other medicinal products on the pharmacokinetics of esomeprazole
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 CYP 3A4 may result in more than doubling of the esomeprazole activity. However a dose adjustment of esomeprazole is not regularly required in either of these situations.

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.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: B

Women with childbearing potential / Contraception
No interaction with contraceptives is expected.

Pregnancy
For esomeprazole, limited data on exposed pregnancies are available. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised if prescribing esomeprazole to pregnant women is absolutely necessary.

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

Reproduction ability / Fertility
No information is available on the effect of esomeprazole with respect to fertility.

4.7 Effects on ability to drive and use machines
No known effect on driving and the use of machine.

4.8 Undesirable effects
The following adverse drug reactions have been identified or suspected in the clinical trials for esomeprazole administered orally or intravenously and post-marketing studies when administered orally.

The reactions are classified according to frequency: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis, pancytopenia

Immune system disorders
Rare: Hypersensitivity reactions e.g angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders
Uncommon: Peripheral oedema
Rare: Hyponatremia
Very rare: Hypomagnesemia

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 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
Very rare: 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
Common: Administration site reactions*
*Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours). Non-clinical program with esomeprazole intravenous formulation indicated no vaso-irritation, but a slight tissue inflammation reaction occurred in the injection site following subcutaneous (paravenous) injection. Nonclinical findings indicate that clinical tissue irritation is related in some sort to concentration.

Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

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

Reproductive system and breast disorders
Very rare: Gynaecomastia

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

Additional information on special populations

Pediatric population
A randomised, 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 (see section 5.2). The safety results are consistent with the known safety profile of esomeprazole, and no new safety signals were identified.

4.9 Overdose and therapy
There is very limited experience to date with 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 utilized.

5.PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: 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-isomer of omeprazole have similar pharmacodynamic activity.

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

Effect on gastric acid secretion
After 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 patients with symptomatic gastro-oesofageal refflux disease. 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 intravenous administration of 80 mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23.5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours and 11-13 hours, respectively, over 24 hours in healthy subjects.

Therapeutic effects of acid inhibition
Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.

In a randomised, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding were randomised to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group (p=0,0256). At 7 days and 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group was 7.2% vs 12.9% (p=0,0096) and 7.7% vs 13.6% (p=0,0092)respectively.

Other effects related to acid secretion
During treatment with antisecretory medicinal product, serum gastrin increases in response to the decreased acid secretion. Chromogranin A (CgA) also increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped at least 5 days before CgA measurement.

An increased number of Enterochromaffin-like cells (ECL) possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment

with orally administered esomeprazole.

During long-term oral treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible. Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Comparative Clinical Trials
In a 5-arm cross-over study, oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg were administered once daily and 24-hour intragastric pH profile was evaluated with 24 symptomatic GORD patients. On day 5, intragastric pH continued over 15.3 hours with esomeprazole, 13.3 hours with rabeprazole, 12.9 hours with omeprazole, 12.7 hours with lansoprazole, and 4.0 over 11.2 hours with pantoprazole ($p \leq 0.001$ for differences between esomeprazole and all other comparisons). Esomeprazole also maintained a higher pH than the other proton pump inhibitors at a significantly higher rate than 4.0 ($p < 0.05$).

Pediatric population:
The effects on intragastric pH following repeated oral administration of esomeprazole 0.5 mg / kg and 1.0 mg / kg in <1 month old and 1 to 11 month old infants, respectively, was comparable with that observed following 20 mg esomeprazole administration in adults, explained by the change in percentage from intragastric pH> 4 since baseline. In addition, 0.5 mg / kg and 1.0 mg / kg esomeprazole resulted in a marked reduction in esophageal acid exposure in in <1 month old and 1 to 11 month old infants.

The safety profile appeared to be similar to that seen in adults.
In a study in paediatric GORD 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:
Absorption after intravenous injection / infusion is 100%.

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.

Metabolism and Elimination:
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.
The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once daily dosing. 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.

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.

Characteristic Properties on Patients
Approximately 3% 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 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.

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

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.

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.

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 GORD patients with severe dysfunction. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

<u>Pediatric population</u>
In a randomised, open-label, multi-national, repeated dose study, esomeprazole was given as a

once-daily 3-minute injection over four days to a total of 50 pediatric patients 0 to 18 years old to evaluate the pharmacokinetics of esomeprazole.

The esomeprazole exposure observed after intravenous administration of esomeprazole 0.5 mg / kg in patients 0 to 1 month* is lower than observed with 1.0 mg / kg in patients 1 to 11 months, but comparable with that observed with 10 mg in children 1 and 5 years, in children 6 and 11 years and with 20 mg in children 12 and 18 years. Exposure levels with these doses are higher than observed with 20 mg in adults but lower than observed with intravenous administration of 40 mg esomeprazole. Esomeprazole exposure after intravenous esomeprazole administration at 1.0 mg / kg for children aged 1 to 11 months, 20 mg for children aged 6 to 11 years and 40 mg for adolescents aged 12 to 18 years was similar to that observed after administration of 40 mg intravenous esomeprazole in adults.

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.

* 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.

5.3 Preclinical safety data
Preclinical studies reveal no particular hazard for humans, based on conventional studies of single and repeated dose toxicity, embryo-foetal toxicity and mutagenicity.

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. Non-clinical program with esomeprazole intravenous formulation indicated no vaso-irritation, but a slight tissue inflammation reaction occurred in the injection site following subcutaneous (paravenous) injection (See Section 4.8).

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Disodium edetate
Sodium hydroxide
Water for injection

6.2 Incompatibilities
The degradation of the reconstituted solution is largely dependent on pH and therefore the product should only be prepared with 0.9% sodium chloride as specified for intravenous use in Section 4.2. Reconstituted solution should not be mixed with another drug and should not be given with another drug in the same infusion set.

6.3 Shelf Life
24 months

Shelf life after reconstitution

Chemical and physical stability of reconstituted solution has been demonstrated for 12 hours at 25°C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage
Keep ESSİUM vial in outer carton, in order to protect from light. Vials can however, be stored exposed to normal indoor light outside the box for up to 24 hours.
Do not store above 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 25°C.

6.5 Nature and contents of container
1 piece in 6 ml Type I colorless glass vial with a bromobutyl rubber stopper and a flip-off transparent cap, in a box.

6.6 Special precautions for disposal and other handling
Do not throw away drugs that have expired or are not used! Deliver to the collection system determined by the Ministry of Environment and Urbanism.

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used. For single use only. Use the half of the reconstituted solution to deliver a dose of 20 mg. Any unused solution must be discarded.

Injection 40 mg
A solution for injection (8 mg/ml) is prepared by adding 5 ml of 0.9% sodium chloride for intravenous use to the esomeprazole 40 mg vial.
The reconstituted solution for injection is clear and colorless to very slightly yellow.

Infusion 40 mg
A solution for infusion is prepared by dissolving the contents of two vials of esomeprazole 40 mg in up to 100 ml of 0.9% sodium chloride for intravenous use.
The reconstituted solution for infusion is clear and colorless to very slightly yellow.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization: 23.05.2018
Date of renewal of the authorization: -
10. DATE OF REVISION OF THE TEXT