SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ESOBLOK 40 mg Powder for Solution for IV Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Active substance:
Esomeprazole 40 mg (as 42.5 mg esomeprazole sodium)

Excipients:
Disodium edetate dihydrate 1.50 mg
Sodium hydroxide q.s.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection and infusion.
White to yellowish-white lyophilized mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- ESOBLOK injection and infusion is indicated as an alternative to the oral therapy, when oral therapy is not possible.

Adults:
- In gastro-esophageal reflux disease (GERD) in patients with esophagitis and/or severe symptoms of reflux.
- In healing of gastric ulcers associated with NSAID therapy.
- In prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

- It is indicated in short-term maintenance of hemostasis and prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Children and adolescents between 1-18 years:
- Gastric antisecretory treatment when the oral medication is not possible, such as:
- Gastro-esophageal reflux disease (GERD) in patients with erosive reflux esophagitis and/or severe symptoms of reflux.

4.2 Posology and Method of Administration

Posology/duration and frequency 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 ESOBLOK

once daily. Patients with reflux esophagitis 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.

Maintaining short-term hemostasis and 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).

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 or half of the reconstituted solution (8 mg/ml) should be given as an intravenous injection when given a 20 mg dosage, 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 regarding 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
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 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 ESOBLOK for infusion, a continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be administered (see section 5.2).

Pediatric population

Posology/frequency of administration and duration

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: once daily 10 mg Weight ≥20 kg: once daily 10 mg or 20 mg	Once daily 10 mg
12-18 years	Once daily 40 mg	Once daily 20 mg

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 or half of the reconstituted solution (8 mg/ml) should be given as an intravenous injection when given a 20 mg dosage, 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 of this medicinal product.
Esomeprazole should not be used concomitantly with drugs like nelfinavir or atazanavir (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, hematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with ESOBLOK 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 metabolized through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (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.

Hypomagnesaemia:
Severe symptomatic and asymptomatic hypomagnesemia has been reported in patients treated with PPIs for at least three months, and in most cases for a year. Serious side effects include tetany, arrhythmias, and seizures. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Interactions with 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. Providers should 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.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamics interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg orally 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%. In light of this data, concomitant use of esomeprazole and clopidogrel should be avoided (see section 4.5).

Sodium warning:
This medicinal product contains less than 1 mmol (23 mg) sodium. No side effects are to be expected in this dosage range for sodium.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Effects 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 metabolizing enzyme. Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is clinically irrelevant. Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients, dose reduction was not necessary in this study.

In a clinical study concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent

R-isomer of warfarin, the coagulation times were within the accepted range. However, in post marketing researches performed with oral esomeprazole, few isolated cases of elevated INR (International Normalized Ratio) of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring of warfarin plasma levels is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamics interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg orally 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%.

Results from a number of observational studies are inconsistent with regard to increased risk or no increased risk for CV thromboembolic events when clopidogrel is given together with a 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 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, likely due to the concomitant administration of low dose ASA.

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

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

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 coadministration 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 qd without

omeprazole 20 mg qd. 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 qd). Treatment with omeprazole 20 mg qd 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. Due to the similar pharmacodynamics effects and with atazanavir and nelfinavir is contraindicated.

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

Effects of esomeprazole on the pharmacokinetics of other medicinal products:
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 like voriconazole may result in more than doubling of the esomeprazole effect. A dose adjustment of esomeprazole was not 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 Fertility, Pregnancy and Lactation

General principles
Pregnancy category is B.

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

Pregnancy
For esomeprazole, limited data on use of pregnancies are available. 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 if it is necessary to prescribe to pregnant women.

Lactation
It is unknown whether esomeprazole is excreted in human milk. No studies have been conducted on nursing mothers. ESOBLOK should not be used during breast-feeding.

Fertility
There is no information regarding the effect of esomeprazole on fertility.

4.7 Effects on ability to drive and use machines
Esomeprazole has no effect the ability to drive or use machines.

4.8 Undesirable effects

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

The undesirable effects are listed below according frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to < 1/100), rare (≥1/10000 to <1/1000) and very rare (<1/10000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	
Rare:	Leucopenia, thrombocytopenia
Very rare:	Agranulocytosis, pancytopenia
Immune system disorders	
Rare:	Hypersensitivity reactions e.g., angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	
Uncommon:	Peripheral edema
Rare:	Hypernatremia
Very rare:	Hypomagnesaemia
Psychiatric disorders	
Uncommon:	Insomnia
Rare:	Agitation, confusion, depression
Very rare:	Aggression, hallucinations
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, paresthesia, somnolence
Rare:	Taste disturbance
Eye disorders	
Uncommon:	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
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). 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 was noted. Non-clinical data showed that clinical tissue irritation is somewhat	

concentration-relevant.	
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:	Hip, wrist and spine fracture (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:	Gynecomasty
General disorders and administration site conditions	
Rare:	Malaise, increased sweating

Additional information on special populations

Pediatric population
Esomeprazole was well tolerated in a randomized, open-label, multi-national study, conducted to evaluate the pharmacokinetics of repeated intravenous doses for 4 days of once daily esomeprazole in pediatric patients between 0 to 18 years (see section 5.2). The safety results are consistent with the known safety profile of esomeprazole, and no new safety signals were identified.

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 to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99).

4.9 Overdose
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 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:
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, 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 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 esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.

In a randomized, double blind, placebo-controlled clinical study, 764 patients with endoscopically confirmed peptic ulcer bleeding were randomized to receive esomeprazole as infusion (n=375) or placebo (n=389). Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received 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 IV treated group compared to 10.3% for the placebo group. At 7 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 inhibition:
During treatment with antisecretory drugs, 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 tumors. Esomeprazole treatment should be stopped temporarily at least 5 days before CgA measurement.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients 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 hospitalized patients, possibly also *Clostridium difficile*.

Comparative clinical studies:
In a randomized, open-label, comparative five-way crossover study evaluated the 24-h intragastric pH profile of oral esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg once daily in GERD patients. On day 5, intragastric pH was maintained above 4.0 for a mean of 15.3 h with esomeprazole, 13.3 h with rabeprazole, 12.9 h with omeprazole, 12.7 h with lansoprazole, and 11.2 h with pantoprazole ($p \leq 0.001$ for differences between esomeprazole and all other comparators). Esomeprazole also provided a significantly higher percentage of patients with an intragastric pH greater than 4.0 relative to the other proton pump inhibitors ($p<0.05$).

Pediatric population
Results from the pediatric studies show that 0.5 mg/kg and 1.0 mg/kg repeated daily oral dosages of esomeprazole in <1 month old and 1 to 11 month old infants, respectively, reduced the mean percentage of time with intra-esophageal pH <4 and were comparable to those observed in adult patients at the 20 mg esomeprazole doses. In addition 0.5 mg/kg and 1.0 mg/kg esomeprazole treatment decreased the esophageal acid exposure in <1 month old and 1 to 11 month old infants significantly. The safety profile appeared to be similar to that seen in adults.

In a study in pediatric 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

General characteristics
Absorption:
Absorption following 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 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.

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. 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 feces. Less than 1% of the parent drug is found in urine.

Characteristics in patients
Approximately 3% 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 oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolizers than in subjects with a functional CYP2C19 enzyme (extensive metabolizers). 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 GERD 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 randomized, open-label, multi-national, repeated dose study, esomeprazole PK was evaluated following a once-daily 3-minute injection in a total of 57 pediatric patients 0 to 18 years old, inclusive.

The esomeprazole exposure following a 0.5 mg/kg intravenous administration to 0-1 month old patients* was lower than in observed in 1-11 month old patients at 1.0 mg/kg but was similar to those observed in 1-5 years at 10 mg, 6-11 years at 10 mg and 12-18 years at 20 mg. The exposure

at these dosages was higher than observed in adults at 20 mg but lower than 40 mg esomeprazole intravenous administration. The esomeprazole exposures following a 1.0 mg/kg intravenous administration to 1-11 month old patients, children from 6-11 years at 20 mg, and adolescents from 12-18 years at 40 mg esomeprazole intravenous administration was similar to those observed in adults following a 40 mg esomeprazole intravenous administration.

Model based predictions indicate that $C_{ss\text{-}max}$ 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-fetal 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 hypergastrinemia 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 was noted. See section 4.8.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium EDTA
Sodium hydroxide

6.2 Incompatibilities
Degradation of reconstituted solution is highly dependent on pH and therefore should only be prepared with 0.9% sodium chloride for intravenous administration as stated in section 4.2. The solution ready for use should not be mixed with any other drug and should not be given together with any other drug in the same infusion.

6.3 Shelf life
24 months.

Shelf-life after reconstitution:
Chemical and physical in-use stability 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 out of the reach and sight of children.

Store at room temperature below 25°C in its original package, in order to protect from light.
Product is prepared for use with adding 5 ml 0.9% NaCl solution or up to 100 ml 0.9% NaCl solution. Prepared solutions are chemically and physically stable at 25°C for 12 hours. From a microbiological point of view, the product should be used immediately.

6.5 Nature and contents of container
Each carton contains one 6 ml Type I colorless glass vial with a gray, scored bromobutyl rubber stopper and sealed with yellow aluminum flip-off cap.

6.6. Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

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.
For 20 mg dosage, the half of the prepared solution should be used. Any unused solution should be discarded.

Injection 40 mg:
A solution for injection (8 mg/ml) is prepared by adding 5 ml of 0.9% sodium chloride solution (for intravenous use) to 40 mg esomeprazole. 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 content of one vial with 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

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.No:1
34303 Küçükçekmece-İSTANBUL

8. MARKETING AUTHORIZATION NUMBER

2014/897

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 17.12.2014
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

29.12.2014