# SUMMARY OF PRODUCT CHARACTERISTICS
# NULOC IV
[Esomeprazole for injection 40 mg]

## 1. NAME OF THE MEDICINAL PRODUCT

NULOC IV (Esomeprazole for Injection 40 mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Esomeprazole Sodium (Lyophilized)

Eq. to Esomeprazole -------- 40 mg

## 3. PHARMACEUTICAL FORM

Powder for injection (For I.V. use only)

White to Off-white free flowing powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Esomeprazole 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 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

<u>Posology</u>

*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.

*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.

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 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. See section 6.3 for shelf-life of the reconstituted solution.).

Special Population

*Patients with impaired renal function*

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.

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 Esomeprazole for infusion, a continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient.

*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<br>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 preparation of reconstituted solution.

**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

**4.3 Contraindications**

Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients. 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 Tablet may alleviate symptoms and delay diagnosis.

Long term use

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

On demand treatment

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.

*Helicobacter pylori* eradication

When prescribing esomeprazole for eradication of Helicobacter pylori possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other active substances metabolised via CYP3A4 such as cisapride.

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 drugs that may cause hypomagnesaemia (e.g., diuretics), health care 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 recognized 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.

Combination with other medicinal products

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.

When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.

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.

Sucrose

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

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least five days before CgA measurements**.** If CgA and gastrin levels have not returned to reference range

after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

**4.5 Interaction with other medicinal products and other forms of interaction**

*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 CYP 2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, $C_{max}$ and $C_{min}$). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, $C_{max}$ and $C_{min}$by 36–39 % and mean AUC, $C_{max}$ and $C_{min}$ for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended 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 drug 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 other medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these active substances may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy.

*Diazepam*

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

*Phenytoin*

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

*Voriconazole*

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C and AUC 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 and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

*Cisapride*

In healthy volunteers, concomitant administration of 40 mg esomeprazole 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 administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

*Clopidogrel*

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggression by an average of 14%.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups. Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

*Investigated medicinal products with no clinically relevant interaction*

*Amoxicillin and quinidine*

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

*Naproxen or rofecoxib*

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

**Effects of other medicinal products on the pharmacokinetics of esomeprazole**

*Medicinal products which inhibit CYP2C19 and/or CYP3A4*

Esomeprazole is metabolised 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 CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

*Medicinal products which induce CYP2C19 and/or CYP3A4*

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

*Paediatric population*

Interaction studies have only been perform in adults.

## 4.6 Pregnancy and lactation

***Pregnancy & 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 or use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported. If affected patients should not drive or use machines.

**4.8 Undesirable effects**

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency (very common > 1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥1/10000 to <1/1000; very rare <1/10000); 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. fever, angioedema and anaphylactic reaction/shock

**Metabolism and nutrition disorders**

Uncommon: Peripheral oedema

Rare: Hyponatraemia

Not known: Hypomagnesaemia; 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.

**Musculoskeletal and connective tissue disorders**

Uncommon: Fracture of the hip, wrist or spine.

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

**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 utilized.

## 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 acidicenvironment 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 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.

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 characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) 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. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group was 7.7% vs 13.6%.

During treatment with antisecretory medicinal products, serum gastrin 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 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*.

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 (double-blind, 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

**Distribution**

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

**Biotransformation**

Esomeprazole is completely metabolised by the cytochrome P450 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. There is a dose-linear increase in total exposure following intravenous administration of esomeprazole as a 30-minute infusion (40 mg, 80 mg or 120 mg) followed by a continuous infusion (4 mg/h or 8 mg/h) over 23.5 hours.

**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. 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.

***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.

| Age group | Dose group | AUC (µmol*h/l) | $C_{ss,max}$ (µmol/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)<br>20 mg (n=6)** | 14.4 (7.2-42.3)<br>10.1 (7.2-13.7) | 8.8 (3.4-29.4)<br>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) |

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.

* 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 was noted.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in reconstitution.

### 6.3 Shelf life

24 months

Shelf life after reconstitution

Chemical and physical in-use stability data has been demonstrated for 12 hours at 30°C. From 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 24 hours at 2-8°C, unless reconstitution has taken place in controlled and aseptic conditions.

### 6.4 Special precautions for storage

Store at a temperature below 30ºC. Protect from Light & moisture.

Keep the medicine out of the reach and sight of children

### 6.5 Nature and contents of container

40 mg Labelled Sterile powder for injection filled in 10ml clear colorless glass vial duly labeled sealed with flip-off seal, along with one plastic ampoule of 10ml WFI in a tray, packed in a printed mono carton along with package insert.

### 6.6 Special precautions for disposal and other handling

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used. The solution has a pH of 9.00-12.00. The osmolality is between 300 and 350 mOsm. For single use only.

If the entire reconstituted content of the vial is not required, any unused solution should be

discarded in accordance with local requirements.

Injection 40 mg

A solution for injection (8 mg/ml) is prepared by adding 5 ml of dissolving solvent provided with this pack for intravenous use to the esomeprazole 40 mg vial.

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.

## 7. MARKETING AUTHORISATION HOLDER

Alkem Laboratories Limited
ALKEM HOUSE, "Devashish",
Senapati Bapat Marg,
Lower Parel, Mumbai – 400 013.
INDIA

## 8. LEGAL CATEGORY

Prescription Only Medicine

## 9. NUMBER AND DATE OF REVISION OF THE TEXT

SPC/NUL/INJ/KN/229-00, Aug 2019.