## 1. NAME OF THE MEDICINAL PRODUCT

Esoprim Control 20 mg gastro-resistant hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant hard capsule contains 20 mg esomeprazole (as sodium).

Excipient(s) with known effect
Each gastro-resistant hard capsule contains about 20.0-22.9mg sucrose.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule. (Gastro-resistant capsule).

Hard capsules with opaque light pink cap and body and printed in black, both, on the cap and on the body (ES on the cap/ 20 on the body).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Esoprim Control is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

### 4.2 Posology and method of administration

Posology
The recommended dose is 20 mg esomeprazole (one capsule) per day.

It might be necessary to take the capsules for 2-3 consecutive days to achieve improvement of symptoms. The duration of treatment is up to 2 weeks. Once complete relief of symptoms has occurred, treatment should be discontinued.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

*Special populations*
*Patients with 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).

*Patients with hepatic impairment*
Dose adjustment is not required in patients with mild to moderate liver impairment. However, patients with severe liver impairment should be advised by a doctor before taking Esoprim Control (see sections 4.4 and 5.2).

*Elderly patients (≥65 years old)*
Dose adjustment is not required in elderly patients.

*Paediatric population*
There is no relevant use of Esoprim Control in the paediatric population below 18 years of age for the indication of "short-term treatment of reflux symptoms (e.g., heartburn and acid regurgitation)".

Method of administration
The capsules should be swallowed whole with half a glass of water. The capsules must not be chewed, crushed or opened.

## 4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients listed in section 6.1.

Esomeprazole must not be used concomitantly with nelfinavir (see section 4.5).

## 4.4 Special warnings and precautions for use

General
Patients should be instructed to consult a doctor if:

- They have significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena and when gastric ulcer is suspected or present, malignancy should be excluded as treatment with esomeprazole may alleviate symptoms and delay diagnosis.
- They have had previous gastric ulcer or gastrointestinal surgery.
- They have been on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should not take Esoprim Control as a long term preventive medicinal product.

Treatment with proton pump inhibitors (PPIs) may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella and Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile* (see section 5.1).

Patients should consult their doctor before taking this medicinal product if they are due to have an endoscopy or urea breath test.

Combination with other medicinal products
Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a PPI is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir.

Esomeprazole 20 mg should not be exceeded.

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

Patients should not take another PPI or $H_2$ antagonist concomitantly.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours.
To avoid this interference, Esoprim Control treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

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 Esoprim Control. 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 sugar spheres (sucrose). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

## 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 medicinal products
As esomeprazole is one enantiomer of omeprazole it is reasonable to advise about interactions reported with omeprazole.

*Protease inhibitors*
Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, $C_{max}$, and $C_{min}$). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once a day) 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 a day without omeprazole 20 mg once a day. Co-administration of omeprazole (40 mg once a day) 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 (see section 4.3 and 4.4).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once a day). Treatment with omeprazole 20 mg once a day had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir).

Treatment with esomeprazole 20 mg once a day had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once a day 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 the dose 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. The absorption of medicinal products taken orally such as ketoconazole, itraconazole and erlotinib can decrease during treatment with esomeprazole 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 monitoring of digoxin should then be reinforced.

*Medicinal products metabolised by CYP2C19*

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as warfarin, phenytoin, citalopram, imipramine, clomipramine, diazepam, etc., the plasma concentrations of these medicinal products may be increased and a dose reduction could be needed. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

*Warfarin*

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical study 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 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 a study in healthy subjects, there was a decreased exposure by almost 40% of the active metabolite of clopidogrel when a fixed dose combination of esomeprazole 20 mg + acetylsalicylic acid 81 mg was given with clopidogrel compared to clopidogrel alone. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in both groups.

Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

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

*Voriconazole*
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) $C_{max}$ and $AUC_{\tau}$ by 15% and 41%, respectively.

*Cilostazol*
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased $C_{max}$ and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

*Cisapride*
In healthy volunteers, concomitant administration of 40 mg esomeprazole 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.

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

*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 and 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 twice a day (b.i.d.)), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the

esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole $AUC_t$ by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

*Medicinal products which induce CYP2C19 and/or CYP3A4*
Medicinal products known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort *(Hypericum perforatum)*) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure**,** it is preferable to avoid the use of Esoprim Control during pregnancy.

Breast-feeding
It is unknown whether esomeprazole/metabolites are excreted in human 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 and visual disturbances are uncommon (see section 4.8). If affected, patients should not drive or use machines.

## 4.8 Undesirable effects

Summary of the safety profile
Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical studies (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions
The following adverse reactions have been identified or suspected in the clinical studies programme for esomeprazole and post-marketing. The reactions are classified according to MedDRA frequency convention: 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).

| | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | | leukopenia, thrombocytope-nia | agranulocytosis, pancytopenia | |
| Immune system | | | hypersensitivity | | |

| | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|
| disorders | | | reactions e.g. fever, angioedema and anaphylactic reaction/shock | | |
| Metabolism and nutrition disorders | | peripheral oedema | hyponatraemia | | hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia; hypomagnesaemia may also result in hypokalaemia |
| Psychiatric disorders | | insomnia | agitation, confusion, depression | aggression, hallucinations | |
| Nervous system disorders | headache | dizziness, paraesthesia, somnolence | taste disturbance | | |
| Eye disorders | | | blurred vision | | |
| Ear and labyrinth disorders | | vertigo | | | |
| Respiratory, thoracic and mediastinal disorders | | | bronchospasm | | |
| Gastrointestinal disorders | abdominal pain, constipation, diarrhoea, flatulence, nausea/ vomiting, fundic gland polyps (benign) | dry mouth | stomatitis, gastrointestinal candidiasis | | microscopic colitis |
| Hepatobiliary disorders | | increased liver enzymes | hepatitis with or without jaundice | hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease | |
| Skin and subcutaneous tissue disorders | | dermatitis, pruritus, rash urticaria | alopecia, photosensitivity | erythema multiforme, Stevens- | Subacute cutaneous lupus |

| | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|
| | | | | Johnson syndrome, toxic epidermal necrolysis (TEN) | erythematosus (see section 4.4). |
| Musculoskeletal and connective tissue disorders | | | arthralgia, myalgia | muscular weakness | |
| Renal and urinary disorders | | | | Interstitial nephritis | |
| Reproductive system and breast disorders | | | | gynaecomastia | |
| General disorders and administration site disorders | | | malaise, increased sweating | | |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/.

### 4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg esomeprazole were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialysable. Treatment should be symptomatic and general supportive measures should be utilised.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, proton pump 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
After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid

output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five 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 gastroesophageal reflux disease (GERD) patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54%, and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92%, and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

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 some patients during long-term treatment with esomeprazole.

Decreased gastric acidity due to any means including PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile*.

Clinical efficacy

Esomeprazole 20 mg has been demonstrated to effectively treat frequent heartburn in subjects receiving one dose per 24 hours over 2 weeks. In two multicentre, randomised, double-blind, placebo-controlled pivotal studies 234 subjects with a recent history of frequent heartburn were treated with 20 mg esomeprazole for 4 weeks. Symptoms associated with acid reflux (such as heartburn and acid regurgitation) were evaluated retrospectively over a 24 hour period. In both studies esomeprazole 20 mg was significantly better compared to placebo for the primary endpoint, complete resolution of heartburn, defined as no heartburn episodes during the last 7 days prior to the final visit (33.9% - 41.6% vs. placebo 11.9 - 13.7%, ($p<0.001$). The secondary endpoint of complete resolution of heartburn, defined as no heartburn on the patient's diary card for 7 consecutive days, was statistically significant at both week 1 (10.0% - 15.2% vs. placebo 0.9% - 2.4%, $p = 0.014$, $p<0.001$) and week 2 (25.2% - 35.7% vs. placebo 3.4% - 9.0%, $p<0.001$).

Other secondary endpoints were supportive of the primary endpoint, including relief of heartburn at week 1 and week 2, percentage of 24 hour days without heartburn at week 1 and week 2, mean heartburn severity at week 1 and week 2, and time to initial and sustained resolution of heartburn over a 24 hour period and during the night compared to placebo. Approximately 78% of the subjects on 20 mg esomeprazole reported first resolution of heartburn within the first week of treatment compared to 52 - 58% for placebo. Time to sustained resolution of heartburn, defined as when 7 consecutive days of no heartburn was first recorded, was significantly shorter in the esomeprazole 20 mg group (39.7% - 48.7% by day 14 vs. placebo 11.0% - 20.2%). The median time to first resolution of night-time heartburn was 1 day, statistically significant compared to placebo in one study ($p=0.048$) and approaching significance in the other ($p=0.069$). About 80% of nights were heartburn free during all time periods and 90% of nights were heartburn free by week 2 of each clinical study, compared to 72.4 - 78.3% for placebo. The investigators' assessments of heartburn resolution were consistent with the subjects' assessments, showing statistically

significant differences between esomeprazole (34.7% - 41.8%) compared to placebo (8.0% - 11.4%). The investigators also found esomeprazole to be significantly more effective than placebo in resolving acid regurgitation (58.5% - 63.6% vs. placebo 28.3% - 37.4%) during the week 2 evaluation.

Following Overall Treatment Evaluation (OTE) of patients at week 2, 78.0 - 80.7% of patients on esomeprazole 20 mg, compared to 72.4 - 78.3% for placebo, reported their condition as improved. The majority of these rated the importance of this change to be Important to Extremely Important in performing their activities of daily living (79 - 86% at week 2).

## 5.2 Pharmacokinetic properties

Absorption
Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

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

Biotransformation
Esomeprazole is completely 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 compound is found in urine.

Linearity/non-linearity
The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Special patient populations
*Poor metabolisers*

Approximately 2.9±1.5% 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 esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were 60% higher.
These findings have no implications for the posology of esomeprazole.

*Gender*
Following a single dose of 40 mg esomeprazole the mean are under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of esomeprazole.

*Hepatic impairment*
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

*Renal impairment*
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

*Elderly patients (≥65 years old)*
The metabolism of esomeprazole is not significantly changed in elderly patients (71-80 years of age).

## 5.3 Preclinical safety data

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Sugar spheres (containing maize starch and sucrose)
Methacrylic acid-ethyl acrylate copolymer
Methyl cellulose
Talc
Triethyl citrate
Glycerol monostearate
Titanium dioxide
Polysorbate 80

Capsule cap:
Hypromellose
Titanium dioxide (E171)
Purified water
Potassium chloride
Carrageenan
Iron oxide red

Capsule body:
Hypromellose
Titanium dioxide (E171)
Purified water
Potassium chloride
Carrageenan
Iron oxide red
Printing ink
Black ink

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

### 6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

### 6.5 Nature and contents of container

The capsules are packed in Aluminium/Aluminium blisters with desiccant packed in a box containing 7 or 14 gastro-resistant capsules.

Not all package sized may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MANUFACTURER

TOWA PHARMACEUTICAL EUROPE, S.L.,
C/DE Sant Martí 75-97,
Martorelles,
08107 Barcelona,
Spain.

## 8. MARKETING AUTHORISATION HOLDER

K.S. KIM INTERNATIONAL LTD,
94 Yigal Alon Str.,
Tel-Aviv-Yafo, 6789139.

## 9. MARKETING AUTHORISATION NUMBER(S)

164-75-36169-00

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