EZIUM
(Esomeprazole)

20mg & 40mg

Capsules

COMPOSITION

EZIUM is available for oral administration as:
EZIUM capsules 20mg Each capsule contains:
Esomeprazole… 20mg (As Esomeprazole Magnesium Trihydrate)

EZIUM capsules 40mg Each capsule contains:
Esomeprazole ….40mg (As Esomeprazole Magnesium Trihydrate)

THERAPEUTIC INDICATIONS

Treatment of Gastro esophageal Reflux Disease (GERD)
Healing of Erosive Esophagitis
Esomeprazole is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course of Esomeprazole may be considered.
Maintenance of Healing of Erosive Esophagitis
Esomeprazole is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.
Symptomatic Gastro esophageal Reflux Disease
Esomeprazole is indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults.

Risk Reduction of NSAID-Associated Gastric Ulcer
Esomeprazole is indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (> 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Triple Therapy (ESOMEPRAZOLE plus amoxicillin and clarithromycin)
Esomeprazole, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Esomeprazole is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

DOSAGE AND ADMINISTRATION

The duration of proton pump inhibitor administration should be based on available safety and efficacy data specific to the defined indication and dosing frequency, as described in the prescribing information, and individual patient medical needs. Proton pump inhibitor treatment should only be initiated and continued if the benefits outweigh the risks of treatment.

Indication	Dose	Frequency
Gastro esophageal Reflux Disease (GERD) Healing of Erosive Esophagitis Maintenance of Healing of Erosive Esophagitis	 20 mg or 40mg 20 mg	 Once Daily for 4 to 8 Weeks* Once Daily**
Symptomatic Gastro esophageal Reflux Disease	20 mg	Once Daily for 4 Weeks***
Risk Reduction of NSAID Associated Gastric Ulcer	20 mg or 40 mg	Once Daily for up to 6 months**
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence Triple Therapy Esomeprazole Amoxicillin Clarithromycin	 40 mg 1000 mg 500 mg	 Once Daily for 10 Days Twice Daily for 10 Days Twice Daily for 10 Days
Pathological Hypersecretory Conditions Including Zollinger Ellison Syndrome	40 mg†	‡Twice Daily
Pediatric Use **12 to 17 Year Olds** **Short-term Treatment of GERD**	 20 mg or 40 mg	 Once Daily for up to 8 Weeks

* The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4 to 8 weeks, an additional 4 to 8 weeks of treatment may be considered.
**Controlled studies did not extend beyond six months.
***If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.
†The dosage of Esomeprazole in patients with pathological hypersecretory conditions varies with the individual patient. Dosage regimens should be adjusted to individual patient needs.
‡Doses up to 240 mg daily have been administered.

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.
Patients with hepatic impairment
Dose adjustment is not required in patients with mild to moderate liver impairment.
Elderly patients (≥65 years old)
Dose adjustment is not required in elderly patients.

Method of administration

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

CONTRAINDICATIONS

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients
Esomeprazole must not be used concomitantly with nelfinavir

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Presence of Gastric Malignancy

In adults, symptomatic response to therapy with Esomeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including Esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Esomeprazole if acute interstitial nephritis develops.

Clostridium difficile-Associated Diarrhea

Published observational studies suggest that PPI therapy like Esomeprazole may be associated with an increased risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.
Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with Esomeprazole.

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. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines

Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including esomeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.
Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.
Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Esomeprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Interaction with Clopidogrel

Avoid concomitant use of Esomeprazole with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using Esomeprazole consider alternative anti-platelet therapy.

Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Interaction with St. John's Wort or Rifampin

Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of Esomeprazole with St. John's Wort or rifampin.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 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.

Interaction with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients

Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

DRUG INTERACTIONS

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. 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 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 AUCτ 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.

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.
As a precautionary measure**,** it is preferable to avoid the use of esomeprazole 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.

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. If affected, patients should not drive or use machines.
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, thrombocytopenia	agranulocytosis, pancytopenia	
Immune system disorders			hypersensitivity 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-Johnson syndrome, toxic epidermal necrolysis (TEN)	Subacute cutaneous lupus erythematosus
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. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

There is very limited experience to date with deliberate overdose. The symptoms described 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 dialyzable. Treatment should be symptomatic and general supportive measures should be utilized.

PHARMACOLOGICAL PROPERTIES

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 pharmacodynamics 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*.

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).

Summary of Clinical Studies

Clinical efficacy

Esomeprazole 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).

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.

PRESENTATION

EZIUM (Esomeprazole) Capsules 20mg are available in alu-alu blister pack of 2 x 7 capsules.

EZIUM (Esomeprazole) Capsules 40mg are available in alu-alu blister pack of 2 x 7 capsules.

INSTRUCTIONS

To be sold on the prescription of a registered medical practitioner only.

Protect from sunlight, moisture and heat.

Store below 30°C.

Keep all medicines out of the reach of children.

REGISTRATION NUMBER

Ezium 20 mg Capsules: 035621

Ezium 40 mg Capsules: 035622

M.L. 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

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