ABGRESS-L™

Esomeprazole Magnesium Trihydrate (EC) & Levosulpiride (SR) Capsules

Prescribing information

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

GENERIC NAME

Esomeprazole Magnesium plus Levosulpiride

BRAND NAME

ESOMAC-L Capsules

QUALITATIVE AND QAUNTITATIVE COMPOSITION

ESOMAC-L Capsules

Each capsule contains:

Esomeprazole Magnesium ..... 40 mg

(as enteric-coated pellets)

Levosulpiride ..... 75 mg

(as sustained-release pellets)

DOSAGE FORM AND STRENGTHS

Capsule for oral use contains Esomeprazole Magnesium 40 mg and Levosulpiride 75 mg

CLINICAL PARTICULARS

Therapeutic Indication

ESOMAC-L Capsule is indicated in the treatment of gastroesophageal reflux disease (GERD).

Posology and Method of Administration

One capsule once daily

Method of Administration

The capsule should be swallowed whole with liquid. The capsule should not be chewed or crushed.

Special Populations

Renal impairment

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section Pharmacokinetic Properties).

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded (see section Pharmacokinetic Properties).

Geriatric population

Dose adjustment is not required in the elderly.

Pediatric Population

Safety and effectiveness of ESOMAC-L Capsule in pediatric patients have not been established

Contraindications

ESOMAC-L Capsules are contraindicated in patients with a known hypersensitivity to esomeprazole, levosulpiride or to substituted benzimidazoles or to any excipients used in the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria (see section Undesirable effects).

Esomeprazole should not be used concomitantly with nelfinavir. For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with ESOMAC-L Capsules, refer to the Contraindications section of their package inserts.. This product should not be used whenever stimulation of gastric motility is to be avoided or could be harmful, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction or perforation.

It is also contraindicated in patients with a prolactin-releasing pituitary tumor (prolactinoma), hepatic and renal impairment, epilepsy, manic states, hyperprolactinaemia, porphyria mammary dysplasia, malignant mastopathies pheochromocytoma and patients with cardiac impairment. It is contraindicated in pregnancy and lactation.

Special Warnings and Precautions for Use

Esomeprazole

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 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 drugs 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* (see section Pharmacodynamic Properties).

Absorption of Vitamin B12

Esomeprazole, like 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 (e.g. longer than 3 years).

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 (see section Contraindications).

Clostridium difficile Associated Diarrhea

Published observational studies suggest that proton pump inhibitor (PPI) therapy like esomeprazole may be associated with an increased risk of *Clostridium difficile* associated diarrhea (CDAD), 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.

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, refer to package inserts of those antibacterial agents.

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.

Hypomagnesemia

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 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), healthcare

professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically thereafter.

Combination with other medicines

Co-administration of esomeprazole with atazanavir is not recommended (see section Drug Interactions). 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 medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section Drug Interactions). 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 (see section Drug Interactions).

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.

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.

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 recognised 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.

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.

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.

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 5 days before CgA measurements (see section Pharmacodynamic Properties).

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.

Drug Interactions

Esomeprazole

Effects of esomeprazole on the pharmacokinetics of other medicinal products

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 once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, C_{max}, and C_{min} 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 (see section Special Warnings and Precautions for Use) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section Contraindications).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once daily had no effect on the exposure of lopinavir (with concomitant ritonavir)

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUCτ by 15% and 41%, respectively.

Concomitant Use of Esomeprazole with St John's wort or Rifampin

Medicinal products 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. Avoid concomitant use of St. John's Wort or rifampin with esomeprazole.

Concomitant Use of Esomeprazole with 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.

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, atazanavir, iron salts, mycophenolate mofetil (MMF), 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 medicinal product monitoring of digoxin should then be reinforced.

Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use esomeprazole with caution in transplant patients receiving MMF..

Effects on Hepatic Metabolism/CYP450 Pathways

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased, and a dose reduction could be needed.

This should be considered especially when prescribing esomeprazole for on-demand therapy

Diazepam

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

Phenytoin

Concomitant oral administration of 40 mg esomeprazole and phenytoin 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.

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.

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

Warfarin

Concomitant oral 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 of oral esomeprazole, 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 aggregation 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 or 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 oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), 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 AUCτ 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..

Levosulpiride

- The effects of levosulpiride on GI motility are antagonized by anticholinergic drugs and narcotic analgesics.
- Additive sedative effects can occur when levosulpiride is given with alcohol, sedatives, hypnotics, narcotics or tranquilizers.
- Levosulpiride releases catecholamines in patients with essential hypertension, so it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.
- The risk of cardiac arrhythmias increases on combined use with other drugs that prolong the QT interval including certain antiarrhythmics, other antipsychotics, some non-sedating antihistamines, antimalarials and cisapride.

- Levosulpiride should be avoided with drugs which cause electrolyte abnormalities like diuretics.

Pregnancy

There are limited post-marketing data on the use of levosulpiride in pregnant women. Levosulpiride is not recommended in pregnancy.

Lactation

Studies have shown that levosulpiride enters breast milk. It is not known whether this is harmful to the newborn. Therefore, breast feeding is not recommended for mothers who are taking levosulpiride.

Pediatric Use

Neurological side effects are rare. Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of neurological side effects is higher in young children. Overdosing may cause extra-pyramidal symptoms in children, but other causes should be taken into consideration.

Use in Special Populations

Patient with Renal Impairment

ESOMAC-L Capsules should be used with caution in patients with renal impairment or in those at risk of fluid retention. Patients on prolonged therapy should be reviewed regularly.

Patient with Hepatic Impairment

Since levosulpiride is highly metabolized in the liver, ESOMAC-L Capsules should be not be used in patients with hepatic impairment.

Pregnant Women

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/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing esomeprazole to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section Animal Toxicology or Pharmacology).

Lactating Women

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

Pediatric Use

The safety and effectiveness of this product in pediatric patients has not been established.

Geriatric Use

Of the total number of patients who received esomeprazole in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age. No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Effects on Ability to Drive and Use Machines

Esomeprazole has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) have been reported (see section Undesirable effects). If affected patients should not drive or use machines.

Undesirable Effects

Esomeprazole

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (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 medicinal product reactions have been identified or suspected in the clinical trials programme for esomeprazole administered orally or intravenously and post-marketing when administered orally. The reactions are classified according to frequency: very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable Effect
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
	Not known	Systemic lupus erythematosus
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia (see section Special Warnings and Precautions for Use); 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	Uncommon	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, pancreatitis
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 (see section Special Warnings and Precautions for Use), hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist, or spine (see section Special Warnings and Precautions for Use)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis: in some patients, renal failure has been reported concomitantly
	Not known	Acute kidney injury
Reproductive system and breast disorders	Very rare	Gynaecomastia

General disorders and administration site conditions	Rare	Malaise, increased sweating

Pediatrics

Safety and effectiveness of esomeprazole in pediatric patients have not been established.

Levosulpiride

Levosulpiride was well tolerated; the incidence of adverse events, though not negligible, were mostly mild and treatment discontinuation was infrequent. The most common adverse events were drowsiness/sedation and endocrine effects. Other side effects may include the following:

- Acute muscular dystonia characterized by abnormal movements (twitching, tremor, etc.) of the hands, leg, tongue and facial muscles.
- Increase in plasma prolactin levels manifested by breast enlargement, production of milk, and stopping of menstrual periods. This can be taken care of with the use of lower dose of this drug. Adverse effects reported with levosulpiride also include, amenorrhoea and change in libido.
- Neuroleptic malignant syndrome (characterized by muscle rigidity, suggestive of muscle damage).
- Akathisia (uncontrollable desire to move about without any anxiety).
- Tardive dyskinesia, it occurs late in the therapy and its features include involuntary rhythmical movements of the face, mouth and jaw.
- Weight gain.

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. If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 1800 267 7779. By reporting side-effects, you can help provide more information on the safety of this product.

Overdosage

Esomeprazole

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. 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 utilised.

Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience.

Levosulpiride

There has been no experience with large overdose of levosulpiride. No specific antidote is known. Treatment in case of overdose should be symptomatic and supportive. The stomach should be emptied by aspiration and lavage. Vital parameters should be managed symptomatically. Emetics should not be used.

At higher doses and in patients sensitive to neuroleptics, overdose may include extrapyramidal effects and sleep disturbances. Anticholinergics or antiparkinson drugs or antihistaminics with anticholinergic properties may be helpful in controlling the extrapyramidal reactions.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Esomeprazole

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.

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.

Levosulpiride

Levosulpiride is a prokinetic agent with dual mechanism of action. It blocks the enteric dopamine (D_2) receptors (both neuronal & muscular) and also acts as an agonist at serotonin (5-HT_4) receptor. Both the above actions increase the release of acetylcholine

(Ach). Ach increases GI peristalsis and also increases lower esophageal sphincter pressure thereby preventing reflux of GI contents towards esophagus. It also inhibits transient lower esophageal sphincter pressure thereby preventing reflux of GI contents towards esophagus. It also inhibits transient lower esophageal sphincter relaxations (TLESRs).

Pharmacodynamic Properties

Esomeprazole

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 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 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.

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

One week's treatment with esomeprazole 20 mg twice daily and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.

After eradication treatment for one week, there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

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 esomeprazole. The findings are considered to be of no clinical significance.

During long-term oral treatment with antisecretory medicinal products, 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*.

Clinical efficacy

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

Pediatric population

No relevant data is available for esomeprazole in pediatric population

Pharmacokinetic properties

Esomeprazole

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 medicinal product is found in urine.

Linearity/non-linearity

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg twice daily. 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 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%. 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. 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

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

Pediatric population

No relevant data is available for esomeprazole in pediatric population.

Levosulpiride

The peak plasma concentration (C_{max}) for levosulpiride after oral administration of the fixed dose combination of esomeprazole and levosulpiride was found to be between 56-61 ng/ml, occurring over a range of 7.9 to 8.2 hours (T_{max}). The plasma half-life of levosulpiride ranges from 5.3 to 9.5 ng/ml and it is mostly eliminated by the kidneys and

urine. Oligopeptide transporter (pept1) polymorphism contribute to the variability of levosulpiride pharmacokinetics.

NONCLINICAL PROPERTIES

Animal Toxicology or Pharmacology

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:

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.

DESCRIPTION

The active ingredient in ESOMAC-L is Esomeprazole and Levosulpiride.

Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S-and R-isomers. (Initial U.S. approval of esomeprazole magnesium: 2001). Its molecular formula is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis.

The structural formula is:

.

Levosulpiride is a (S)-(-)-5-aminosulfonyl-N-[(1-ethyl-2-pyrrolidinyl) methyl]-2-methoxybenzamide, an (-) enantiomer of sulpiride that exhibits anti-emetic, anti-dyspeptic, anti-psychotic and anti-depressant activities. Levosulpiride specifically blocks dopamine D2 receptors in the central nervous system (CNS) and gastrointestinal (GI) tract.

PHARMACEUTICAL PROPERTIES

Incompatibilities

Not applicable.

Shelf-Life

As on the pack.

Packaging Information

ESOMAC-L Capsules …….. Strip pack of 10 capsules

Storage and Handling Instructions

Store in a cool and dry place. Protect from light.

PATIENT COUNSELLING INFORMATION

1. What is ESOMAC-L Capsules and what is it used for?

ESOMAC-L Capsules contains a medicine called esomeprazole and Levosulpiride.

Esomeprazole belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

It is used to treat the following conditions:

Adults

- 'Gastroesophageal reflux disease' (GERD). This is where acid from the stomach escapes into the food pipe (the tube which connects your throat to your stomach) causing pain, inflammation and heartburn.
- Ulcers in the stomach or upper part of the gut (intestine) that are infected with bacteria called '*Helicobacter pylori*'. If you have this condition, your doctor may also prescribe antibiotics to treat the infection and allow the ulcer to heal.

Children and adolescents aged 1-18 years

Safety and effectiveness of esomeprazole have not been established in pediatric patients.

1. What you need to know before you take esomeprazole?

DO not take esomeprazole:

- If you are allergic to esomeprazole or any of the other ingredients of this medicine.
- If you are allergic to other proton pump inhibitor medicines (e.g. pantoprazole, lansoprazole, rabeprazole, omeprazole).
- If you are taking a medicine containing nelfinavir (used to treat HIV infection).

You must not take esomeprazole if any of the above apply to you. If you are not sure, talk to your doctor or nurse before you are given this medicine.

Warnings and precautions

Talk to your doctor or nurse before you are given esomeprazole if:

- You have severe liver problems.
- You have severe kidney problems.
- You have ever had a skin reaction after treatment with a medicine similar to Esomeprazole that reduces stomach acid.
- You are due to have a specific blood test (Chromogranin A).

Esomeprazole may hide the symptoms of other diseases. Therefore, if any of the following happen to you before you take esomeprazole or after you are given it, talk to your doctor straight away:

- You lose a lot of weight for no reason and have problems swallowing.
- You get stomach pain or indigestion.
- You begin to vomit food or blood.
- You pass black stools (blood-stained faeces).

If you have been prescribed esomeprazole "on demand" you should contact your doctor if your symptoms continue or change in character.

Taking a proton pump inhibitor like esomeprazole, especially over a period of more than one year, may slightly increase your risk of fracture in the hip, wrist, or spine. Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can increase the risk of osteoporosis).

If you get a rash on your skin, especially in areas exposed to the sun tell your doctor as soon as you can, as you may need to stop your treatment with esomeprazole. Remember to also mention any other ill effects like pain in your joints.

Other medicines and esomeprazole

Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines. This includes medicines that you buy without a prescription. This is because esomeprazole can affect the way some medicines work, and some medicines can have an effect on esomeprazole.

You must not be given esomeprazole if you are taking a medicine containing nelfinavir (used to treat HIV infection).

Tell your doctor or nurse if you are taking any of the following medicines:

- Atazanavir (used to treat HIV infection).
- Clopidogrel (used to prevent blood clots).

- Ketoconazole, itraconazole or voriconazole (used to treat infections caused by a fungus).
- Erlotinib (used to treat cancer).
- Citalopram, imipramine or clomipramine (used to treat depression).
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used in epilepsy). If you are taking phenytoin, your doctor will need to monitor you when you start or stop having esomeprazole.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop having esomeprazole.
- Cilostazol (used to treat intermittent claudication – a pain in your legs when you walk which is caused by an insufficient blood supply).
- Cisapride (used for indigestion and heartburn).
- Digoxin (used for heart problems).
- Methotrexate (a chemotherapy medicine used in high doses to treat cancer) – if you are taking a high dose of methotrexate, your doctor may temporarily stop your esomeprazole treatment.
- Tacrolimus (organ transplantation).
- Rifampicin (used for treatment of tuberculosis).
- John's wort (*Hypericum perforatum*) (used to treat depression).

If your doctor has prescribed the antibiotics amoxicillin and clarithromycin as well as esomeprazole to treat ulcers caused by *Helicobacter pylori* infection, it is very important that you tell your doctor about any other medicines you are taking.

Esomeprazole with food and drink

Esomeprazole should be taken at least 1 hour before meals.

Pregnancy, breast-feeding and fertility

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine. Your doctor will decide whether you can take esomeprazole during this time.

It is not known if esomeprazole passes into breast milk. Therefore, you should not be given esomeprazole if you are breastfeeding.

Driving and using machines

Esomeprazole is not likely to affect you being able to drive or use any tools or machines. However, side effects such as dizziness and blurred vision may uncommonly occur. If affected, you should not drive or use machines.

1. How to take esomeprazole?

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- If you are taking this medicine for a long time, your doctor will want to monitor you (particularly if you are taking it for more than a year).
- If your doctor has told you to take this medicine as and when you need it, tell your doctor if your symptoms change.

How much to take

- Your doctor will tell you how many capsule to take and how long to take them for. This will depend on your condition; how old you are and how well your liver works.
- The recommended doses are given below.

Use in adults aged 18 and above

To treat heartburn caused by gastroesophageal reflux disease (GERD):

- If your doctor has found that your food pipe (food pipe) has been slightly damaged, the recommended dose is one esomeprazole 40 mg gastro-resistant tablet once a day for 4 weeks.

Your doctor may tell you to take the same dose for a further 4 weeks if your food pipe has not yet healed.

- The recommended dose once the food pipe has healed is one esomeprazole 20 mg gastro-resistant tablet once a day
- If your food pipe has not been damaged, the recommended dose is one esomeprazole 20 mg gastro-resistant tablet each day. Once the condition has been controlled, your doctor may tell you to take your medicine as and when you need it, up to a maximum of one esomeprazole 20 mg gastro-resistant tablet each day.
- If you have severe liver problems, your doctor may give you a lower dose.

To treat ulcers caused by Helicobacter pylori infection and to stop them coming back:

- The recommended dose is one ESOMAC-L 20 mg gastro-resistant tablet twice a day for one week.

- Your doctor will also tell you to take antibiotics for example amoxicillin and clarithromycin.

To treat stomach ulcers caused by NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):

- The recommended dose is one ESOMAC-L 20 mg gastro-resistant tablet once a day for 4 to 8 weeks.

To prevent stomach ulcers if you are taking NSAIDs (Non-Steroidal Anti-Inflammatory Drugs):

- The recommended dose is one ESOMAC-L 20 mg gastro-resistant tablet once a day.

To treat too much acid in the stomach caused by a growth in the pancreas (Zollinger-Ellison syndrome):

- The recommended dose is ESOMAC-L 40 mg twice a day.
- Your doctor will adjust the dose depending on your needs and will also decide how long you need to take the medicine for. The maximum dose is 80 mg twice a day.

Prolonged treatment after prevention of rebleeding of ulcers with intravenous esomeprazole:

- The recommended dose is one ESOMAC-L 40 mg tablet once a day for 4 weeks.

Taking this medicine

- You should take your tablets at least one hour before taking a meal.
- Swallow your tablets whole with a drink of water. Do not chew or crush the tablets.

Elderly

Dose adjustment is not required in the elderly.

If you take more esomeprazole than you should

If you take more esomeprazole than prescribed by your doctor, talk to your doctor or pharmacist straight away.

1. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following serious side effects, stop taking esomeprazole and contact a doctor immediately:

- Sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing (severe allergic reaction).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

These effects are rare and may affect up to 1 in 1,000 people.

Other side effects include:

Common (may affect up to 1 in 10 people)

-
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).
- Benign polyps in the stomach.

Uncommon (may affect up to 1 in 100 people)

- Swelling of the feet and ankles.
- Disturbed sleep (insomnia).
- Dizziness, tingling feelings such as "pins and needles", feeling sleepy.
- Spinning feeling (vertigo).
- Dry mouth.
- Changes in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.
- Fracture of the hip, wrist or spine (if esomeprazole is used in high doses and over long duration).

Rare (may affect up to 1 in 1,000 people)

- Blood problems such as a reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps.
- Feeling agitated, confused or depressed.

- Eyesight problems such as blurred vision.
- Taste changes.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- An inflammation of the inside of the mouth.
- An infection called “thrush” which can affect the gut and is caused by a fungus.
- Liver problems, including jaundice which can cause yellow skin, dark urine, and tiredness.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pains (arthralgia) or muscle pains (myalgia).
- Generally feeling unwell and lacking energy.
- Increased sweating.

Very rare (may affect up to 1 in 10,000 people)

- Changes in blood count including agranulocytosis (lack of white blood cells)
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- Seeing, feeling or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Muscle weakness.
- Severe kidney problems.
- Enlarged breasts in men.

Not known (frequency cannot be estimated from the available data)

- If you are on esomeprazole for more than three months it is possible that the levels of magnesium in your blood may fall. Low levels of magnesium can be seen as fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate. If you get any of these symptoms, please tell your doctor promptly. Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. Your doctor may decide to perform regular blood tests to monitor your levels of magnesium.

- Inflammation in the gut (leading to diarrhea).
- Rash, possibly with pain in the joints.
- Inflammation of the pancreas (pancreatitis)
- Systemic lupus erythematosus
- Excessive sweating (hyperhidrosis)
- Kidney damage (acute kidney injury)

Esomeprazole may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a severely reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medication at this time.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse write to drugsafety@cipla.com. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 1800 267 7779. By reporting side-effects, you can help provide more information on the safety of this product

1. How to store esomeprazole?
    - Keep this medicine out of reach of children.
    - Store in a cool, dry place. Protect from light.
    - Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
    - Store this medicine in the original package (blister).
    - Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

DETAILS OF MANUFACTURER

Mfd. By Cipla Ltd.

Registered Office:

Cipla House, Peninsula Business Park,

Ganpatrao Kadam Marg

Lower Parel

Mumbai – 400 013, India

DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

PD-458A dated 03/02/2015

DATE OF REVISION

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