

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

IZRA-L

1. Generic Name

Enteric coated Esomeprazole 40 mg & Sustained Release Levosulpiride 75 mg Capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Esomeprazole Magnesium Trihydrate I.P. equivalent to Esomeprazole40mg

(as enteric coated pellets)

Levosulpiride75mg (as sustained release tablet)

Colour: Titanium Dioxide I.P.

Approved colour used in capsule shell.

The excipients used are Microcrystalline Cellulose, Lactose Monohydrate, HPMC K 100 M, Citric Acid Monohydrate, P.V.P.K-30, Magnesium Stearate and Talcum Powder.

3. Dosage form and strength

Dosage form: Capsules

Strength: Esomeprazole 40 mg and Levosulpiride 75 mg

4. Clinical particulars

4.1 Therapeutic indication

For short term therapy of Gastroesophageal Reflux Disease (GERD) in patients who do not respond to PPI alone.

4.2 Posology and method of administration

Adults

Gastroesophageal Reflux Disease (GERD)

- Treatment of erosive reflux esophagitis: The recommended dose is one capsule per day. An additional 4 weeks treatment is recommended for patients in whom esophagitis has not healed or who have persistent symptoms.
- Long-term management of patients with healed esophagitis to prevent relapse: The recommended dose is one capsule per day.
- Symptomatic treatment of gastroesophageal reflux disease (GERD): The recommended dose is one capsule per day in patients without esophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using single capsule once daily.

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.

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, dose shall be adjusted as recommended by physician.

Elderly

Dose adjustment is not required in the elderly.

Method of administration

The capsule should be administered with water in intact form. The capsules must not be chewed, crushed or opened.

4.3 Contraindications

IZRA-L is contra-indicated in:

- Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.
- Esomeprazole should not be used concomitantly with nelfinavir.
- Elderly people
- Children less than 14 years of age
- Parkinson disease
- Severe renal or hepatic insufficiency
- History of epilepsy
- Porphyrias
- Breast cancer
- Alcohol intoxication
- Certain tumors like pheochromocytoma and pituitary prolactinoma
- Hypokalemia
- The drug should be used cautiously in pregnancy (only when it is expected to benefit the mother more than the possibility of risking the fetus).
- The drug is known to be secreted in breast milk, so, its use should be restricted in breastfeeding women.

4.4 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*.

Absorption of vitamin B12

Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other 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.

Combination with other medicinal products

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

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

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. 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.

Levosulpiride

Extrapyramidal reactions, mainly akathisia, and for that dosage reduction warranted. Increased motor agitation at higher dosages. Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in association with other antipsychotic drugs. NMS is associated with hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia).

Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. In such an event, or with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs must be discontinued. If resumption of treatment with antipsychotic drugs becomes essential, the patient should be carefully monitored. Levosulpiride should be used with caution in patients with manic states such as in the manic phase of manic depressive psychosis. Caution is advised when the drug is administered to patients with cerebrovascular events including risk factors for stroke. Caution is also advised when levosulpiride is given to patients with cardiac insufficiency.

Levosulpiride should not be used when gastrointestinal stimulation of motility can be harmful, e.g., in presence of gastrointestinal hemorrhage, mechanical obstructions or perforations. Levosulpiride may cause drowsiness in some patients especially at higher doses, thus patients should be advised to exercise caution when driving or operating machinery. Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects. The dose should be reduced if there is evidence of renal impairment. Caution is advised when there is prolongations of QTc interval or factors that may predispose QTc interval prolongation (Bradycardia, hypokalemia, congenital QTc prolongation, decreased intracardiac conduction) Clinical experience in children under 14 years of age is insufficient to permit specific recommendations.

4.5 Drugs interactions

Esomeprazole

Effects of esomeprazole on the pharmacokinetics of other drugs

Protease inhibitors

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

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36–39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

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

Methotrexate

When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Medicinal products with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on-demand therapy.

Diazepam

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

Phenytoin

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

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C and AUC by 15% and 41%, respectively.

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{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.

Warfarin

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

Clopidogrel

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

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

Naproxen or rofecoxib

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

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased esomeprazole AUC by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4

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

Paediatric population

Interaction studies have only been performed in adults.

Levosulpiride

- Caution is advised when levosulpiride is taken concomitantly with other centrally acting drugs. It can potentiate the cognitive and motor effects of alcohol.
- CNS depressants including narcotics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.
- Lithium increases the risk of extrapyramidal side effects.
- Caution is advised with medications that may predispose QTc interval prolongation that include: Bradycardia inducing medications: Beta blockers, calcium channel blockers (verapamil, diltiazem), clonidine, and digitalis.
- Medications which induce electrolyte imbalance (particularly hypokalemia), hypokalaemic diuretics, stimulant laxatives, IV amphoterecin B, glucocorticoids, and tetracosectides.
- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.

- Other medications such as pimozone, haloperidol; methadone, imipramine, antidepressants; lithium, cisapride, thioridazine, IV erythromycin, halofantrine and pentamidine.
- Antihypertensive agents: antihypertensive effect and possibility of enhanced postural hypotension. The effect of levosulpiride on gastrointestinal motility can be antagonized by anticholinergic drugs; narcotics and analgesic drugs.
- Antacids or sucralfate: The absorption of sulpiride is decreased after co- administration; hence, sulpiride should be administered two hours before these drugs.
- Sulpiride may reduce the effectiveness of ropinorole.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

IZRA-L should not be used during presumed or confirmed pregnancy.

Breast-feeding

IZRA-L should not be used during the lactation period.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects On Ability To Drive And Use Machines

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

4.8 Undesirable effects

Esomeprazole and Levosulpiride

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 drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency very common $\geq 1/10$; common $\geq 1/100$ to $< 1/10$; uncommon $\geq 1/1,000$ to $< 1/100$; rare $\geq 1/10,000$ 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	Rare	Hypersensitivity reactions e.g. fever, angioedema and

disorders		anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Very rare	Weight gain
	Not known	Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Nervous system disorders	Common	Headache
	Very common	Somnolence, Torpor
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
	Very rare	Parkinsonism, Dyskinesia, Tremor, Dystonia, Psychomotor agitation, Disorders of the autonomic nervous system
	Not known	Neuroleptic Malignant Syndrome
Eye disorders	Rare	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis

Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticarial
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
	Not known	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patients renal failure has been reported concomitantly, Acute kidney injury
Reproductive system and breast disorders	Very rare	Gynaecomastia
	Not known	Amenorrhoea, Galactorrhea, Changes in libido
General disorders and administration site conditions	Rare	Malaise, increased sweating
Cardiac disorders	Rare	QT prolongation, Ventricular arrhythmias such as torsades de pointes, Ventricular tachycardia, Ventricular fibrillation, Cardiac arrest
	Very rare	Sudden death
Vascular disorders	Not known	Thromboembolism (including cases of pulmonary embolism and deep venous thrombosis)
Pregnancy, puerperium and perinatal conditions	Not known	Neonatal withdrawal syndrome, Extrapyrarnidal symptoms
Investigations	Not known	Hyperprolactinaemia

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Esomeprazole

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg 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. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Levosulpiride

The medicine can induce extrapyramidal effects and sleep disorders, at higher doses and in patients sensitive to neuroleptics. In these cases it will be advisable to reduce the dosage or discontinue the treatment, according to the physician decision.

5. Pharmacological properties

5.1. Mechanism of Action

Esomeprazole

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 an atypical antipsychotic agent that blocks the presynaptic dopaminergic D2 receptors. Like its parent compound, levosulpiride shows antagonism at D3 and D2 receptors present presynaptically as well as postsynaptically in the rat striatum or nucleus accumbens. The preferential binding of the presynaptic dopamine receptors decreases the synthesis and release of dopamine at low doses whereas it causes postsynaptic D2 receptor antagonism at higher dose. This receptor profile of the drug along with its limbic selectivity explains its effectiveness in the management of both positive and negative symptoms of schizophrenia.

5.2. Pharmacodynamic properties

Esomeprazole

Pharmacotherapeutic group: Drugs for acid-related disorders proton pump inhibitors

ATC code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Mechanism of action

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly 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 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 four weeks, and in 93% after eight weeks.

One weeks treatment with esomeprazole 20 mg b.i.d. 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 treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

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

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.

Paediatric population

In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

Levosulpiride

Biochemical, pharmacological and clinical data obtained with the two isomers of sulpiride, indicate that the antidopaminergic activity, both at central and local levels, is due to levo- rotatory enantiomer.

5.3. 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 drug 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 $2.9 \pm 1.5\%$ 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 increased by about 60%. These findings have no implications for the posology of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean area 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

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

Paediatric population

Adolescents 12-18 years:

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure

(AUC) and the time to reach maximum plasma concentration (t_{\max}) in 12 to 18 year-olds was similar to that in adults for both esomeprazole doses.

Levosulpiride

The parent drug is given in a dose of 400-180 mg orally daily although a much lower dose is effective for producing antidepressant effect (about 50-300 mg). The plasma $t_{1/2}$ of the drug is about 6-8 hours. The drug is chiefly excreted through the renal route.

6. Nonclinical properties

Esomeprazole

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.

Levosulpiride

Studies performed in rats and mice, administering the medicine at a dose higher than that expected for man, have shown that levosulpiride do not possess carcinogenic properties.

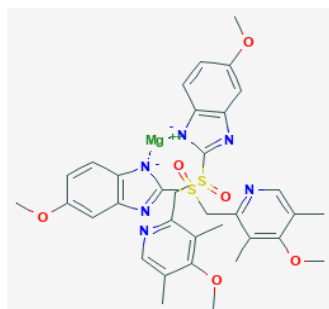
Studies carried out in rats and rabbits have shown that the medicine is not teratogenic.

In vitro tests have ruled out that the medicine possesses mutagenic properties.

7. Description

Esomeprazole

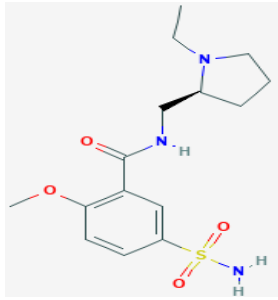
Esomeprazole is bis 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]benzimidazol-1-ide magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole. The molecular formula is $C_{34}H_{36}MgN_6O_6S_2$, and the molecular weight is 713.1 g/mol. The structural formula is:



Esomeprazole Magnesium Trihydrate is white to off-white powder which is soluble in N,N-dimethyl formamide.

Levosulpiride

Levosulpiride is N-[[[(2S)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-5-sulfamoyl]benzamide. The molecular formula is $C_{15}H_{23}N_3O_4S$, and the molecular weight is 341.4 g/mol. The structural formula is:



Enteric coated Esomeprazole 40 mg & Sustained Release Levosulpiride 75 mg Capsules are Yellow colour cap and yellow colour body '0' size, hard gelatin capsules, containing white to off white coloured, round, biconvex, uncoated, plain on both sides, Levosulpiride tablet and white to off white coloured Esomeprazole enteric coated spherical pellets. The excipients used are Microcrystalline Cellulose, Lactose Monohydrate, HPMC K 100 M, Citric Acid Monohydrate, P.V.P.K-30, Magnesium Stearate and Talcum Powder.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

IZRA-L is available in strip of 10 capsules.

8.4 Storage and handing instructions

Store protected from light & moisture at a temperature not exceeding 30°C.

9. Patient counselling information

Package leaflet: information for the patient

IZRA-L

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1. What IZRA-L is and what it is used for

9.2. What you need to know before you take IZRA-L

9.3. How to take IZRA-L

9.4. Possible side effects

9.5. How to store IZRA-L

9.6. Contents of the pack and other information

9.1 What IZRA-L is and what it is used for

IZRA-L is a combination of medicines called esomeprazole and levosulpiride. They work by reducing the amount of acid that your stomach produces. IZRA-L is used as short term therapy of Gastroesophageal Reflux Disease (GERD) in patients who do not respond to PPI alone.

9.2 What you need to know before you take IZRA-L

Do not take IZRA-L if:

- If you are allergic to IZRA-L 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).

Do not take IZRA-L if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking IZRA-L.

Warnings and precautions

Talk to your doctor or pharmacist before taking IZRA-L:

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

IZRA-L may hide the symptoms of other diseases. **Therefore, if any of the following happen to you before you start taking IZRA-L or while you are taking 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 IZRA-L “on demand” you should contact your doctor if your symptoms continue or change in character.

Taking a proton pump inhibitor like IZRA-L, 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 IZRA-L. Remember to also mention any other ill-effects like pain in your joints.

Other medicines and IZRA-L

Tell your doctor or pharmacist 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 IZRA-L can affect the way some medicines work and some medicines can have an effect on IZRA-L.

Do not take Esomeprazole Tablets if you are taking a medicine containing nelfinavir (used to treat HIV infection).

Tell your doctor or pharmacist 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 taking Esomeprazole.
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking 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).
- St. John's wort (*Hypericum perforatum*) (used to treat depression).
- Alcohol and other centrally acting drugs, CNS depressant drugs
- Lithium
- Medicines that cause QTc prolongation
- Medicines that induce electrolyte imbalance
- quinidine and disopyramide
- Drugs used in hypertension
- Drugs used in acidity
- Ropinirole

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

IZRA-L with food and drink

You can take your tablets with food or on an empty stomach.

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 taking this medicine. Your doctor will decide whether you can take IZRA-L during this time. It is not known if IZRA-L passes into breast milk. Therefore, you should not take IZRA-L if you are breastfeeding.

Driving and using machines

IZRA-L is likely to affect you being able to drive or use any tools or machines. If affected, you should not drive or use machines.

9.3 How to take IZRA-L

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 tablets 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.

Taking this medicine

- You can take IZRA-L with food or on an empty stomach.
- Take the IZRA-L as suggested by your doctor or pharmacist

Use in children under the age of 14 years

IZRA-L is not recommended for children less than 14 years old (ask your doctor or pharmacist if you require further information).

Elderly

Dose adjustment is not required in the elderly.

If you take more IZRA-L than you should

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

If you forget to take IZRA-L

- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose.
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 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 IZRA-L 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)

- Headache.
- 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.
- Taste changes.
- Eyesight problems such as blurred vision.
- 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.
- Heart related diseases (eg. QT prolongation, Ventricular arrhythmias such as torsades de pointes, Ventricular tachycardia, Ventricular fibrillation, Cardiac arrest)

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

- Changes in blood count including agranulocytosis (lack of white blood cells)
- Weight gain
- Aggression.
- Seeing, feeling or hearing things that are not there (hallucinations).
- Psychological disease like Parkinsonism, disorders related to movement (eg. Dyskinesia, Tremor, Dystonia, Psychomotor agitation, Disorders of the autonomic nervous system)
- 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, Acute kidney injury
- Enlarged breasts in men.
- Sudden death

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

- If you are on IZRA-L 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 diarrhoea).
- Rash, possibly with pain in the joints.
- Disease related to brain eg. Neuroleptic Malignant Syndrome
- Abnormal absence of menstruation
- Spontaneous flow of milk from the breast, unassociated with childbirth or nursing
- Changes in sexual desire
- Disorder related to blood clot (Thromboembolism)
- Disorders related to pregnancy and new borns (Neonatal withdrawal syndrome, Extraparamidal symptoms)

- High levels of prolactin hormone in blood

IZRA-L 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. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5 How to store IZRA-L

Store protected from light & moisture at a temperature not exceeding 30°C.

9.6 Contents of the pack and other information

The active substances in IZRA-L are Esomeprazole Magnesium and Levosulpiride.

The excipients used in IZRA-L are Microcrystalline Cellulose, Lactose Monohydrate, HPMC K 100 M, Citric Acid Monohydrate, P.V.P.K-30, Magnesium Stearate and Talcum Powder.

10. Details of manufacturer

Manufactured by:

Acme Generics LLP.,

Plot No. 115, HPSIDC Industrial Area, Davni, P.O. Gurumajra,

Tehsil Nalagarh, Dist. Solan, Himachal Pradesh – 174 101.

11. Details of permission or licence number with date

Mfg Lic No. MNB/15/880 issued on 28.09.2015.

12. Date of revision

Not applicable

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/IZRA-L 40,75mg/JUN-20/01/PI