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

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Esomeprazole (GR) & Domperidone (SR) Capsules
(Brand Name: S-RD® Capsules)

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:
Esomeprazole Magnesium Trihydrate IP equivalent to Esomeprazole .....… 40 mg
(as Gastro-resistant pellets)
Domperidone IP …… 30 mg
(as sustained release pellets)
Excipients ……. q.s.
Colours: Sunset Yellow FCF
Colours used in capsule shell : Brilliant Blue FCF, Tartrazine, Titanium Dioxide IP.
Methylparaben and Propylparaben used as Antimicrobial preservatives.

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Esomeprazole 40 mg (in a gastro-resistant form) and domperidone 30 mg (in a sustained release form) per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

S-RD Capsules are indicated for the treatment gastro-esophageal reflux disease (GERD) not responding adequately to esomeprazole alone.

4.2Posology and Method of Administration

<u>For oral administration in adults.</u>
Recommended dose is 1 capsule to be administered once daily for 4 to 8 weeks.
S-RD Capsules should be administered on empty stomach, preferably in the morning or at least 1 hour prior to meal. The capsules should be swallowed whole with water and not to be opened, chewed or crushed.
Or, as prescribed by the physician.

4.3Contraindications

S-RD Capsules are contraindicated in the following:

- Patients with known hypersensitivity to esomeprazole or to any substituted benzimidazole derivative or to domperidone or to any component of the formulation.
- In patients receiving rilpivirine-containing products.
- Prolactin-releasing pituitary tumor (prolactinoma).
- In patients with gastrointestinal hemorrhage, mechanical obstruction or perforation (i.e., when stimulation of the gastric motility could be harmful).
- In patients with moderate or severe hepatic impairment.
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc.
- Patients with significant electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesemia) or underlying cardiac disease such as congestive heart failure (CHF).
- Co-administration with QT-prolonging drugs.
- Co-administration with potent CYP3A4 inhibitors.

4.4Special Warnings and Precautions for Use

Esomeprazole

Gastric Malignancy: 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.

***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/Gastritis: Treatment with proton pump inhibitors (PPIs) may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** Published observational studies suggest that PPI therapy like esomeprazole may be associated with an increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Absorption of Vitamin B_{12}: Esomeprazole, like all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

Risk of Bone Fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose (defined as multiple daily doses), and long-term PPI therapy (a year or longer). Patients should use the

lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines and they should have an adequate intake of vitamin D and calcium.

Subacute Cutaneous Lupus Erythematosus (SCLE): PPIs have been associated with cases of SCLE, although very infrequently. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and esomeprazole therapy should be stopped immediately. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

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

Domperidone

Cardiovascular Effects: Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolongation drugs or CYP3A4 inhibitors.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure (CHF) due to increased risk of ventricular arrhythmia. Electrolyte disturbances or bradycardia are known to be conditions increasing the proarrythmic risk. Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician. Patients should be advised to promptly report any cardiac symptoms.

Use with Apomorphine: Domperidone is contraindicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks.

Use in Infants and Children: Although neurological side effects are rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

4.5Drug Interactions

Esomeprazole

1) Interference with Antiretroviral Therapy

Reduced Concentrations of Atazanavir and Nelfinavir: Concomitant use of atazanavir and nelfinavir with PPIs is not recommended. Co-administration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. If the combination of atazanavir with a PPI is 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.

Increased Concentrations of Saquinavir: Co-administration of saquinavir with PPIs is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with other antiretroviral drugs, too. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19.

2) Drugs for Which Gastric PH Can Affect Bioavailability (ketoconazole, atazanavir, iron salts, erlotinib, mycophenolate mofetil, digoxin)

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability. Like with other drugs that decrease intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole.

Digoxin: Concomitant treatment with omeprazole (20 mg daily), of which esomeprazole is an enantiomer, and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Co-administration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

Mycophenolate Mofetil (MMF): 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.

3) Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Esomeprazole is extensively metabolized in the liver by CYP 2C19 and CYP 3A4. *In-vitro* and *in-vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole

does not have any clinically significant interactions with quinidine, clarithromycin, or amoxicillin.

Warfarin: Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR (International Normalized Ratio) and prothrombin time. Increases in INR and prothrombin time may lead to abnormal bleeding.

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

Diazepam: Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

Phenytoin: Concomitant administration of esomeprazole 40 mg 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.

Cilostazol: Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, of which esomeprazole is an enantiomer, 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 esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (t½), 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.

Voriconazole: Concomitant administration of esomeprazole and a combined inhibitor of CYP 2C19 and CYP3A4, such as voriconazole, may result in a more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses (up to 240 mg/day), dose adjustment may be considered.

Rifampicin: Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Avoid concomitant use of rifampin with esomeprazole.

St. John's Wort: Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's wort, an inducer of CYP3A4. Avoid concomitant use of St. John's wort with esomeprazole.

4) Concomitant Administration with Other Drugs

Tacrolimus: Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

Combination Therapy with Clarithromycin: Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in an increase in plasma levels of esomeprazole and 14-hydroxyclarithromycin.
Methotrexate: Concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, leading to a risk of methotrexate toxicity. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

5) Drug / Laboratory Tests Interactions
Interactions with Investigations of Neuroendocrine Tumors: Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements; consider repeating the test if initial CgA levels are high.

Domperidone
The main metabolic pathway of domperidone is through CYP3A4. *In vitro* data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.
There is increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

1) Concomitant use of the following drugs is contraindicated.

i. QTc-prolonging medicinal products:

- Anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine).
- Anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
- Certain antipsychotics (e.g., haloperidol, pimozide, sertindole).
- Certain antidepressants (e.g., citalopram, escitalopram).
- Certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin).
- Certain antifungal agents (e.g., pentamidine).
- Certain antimalarial agents (e.g., halofantrine, lumefantrine).
- Certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride).
- Certain antihistaminics (e.g., mequitazine, mizolastine).
- Certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine).
- Other medicines (e.g., bepridil, diphemanil, methadone).

ii. Potent CYP3A4 inhibitors (regardless of their QT prolonging effects):

- Protease inhibitors.
- Systemic azole antifungals.
- Some macrolides (e.g., erythromycin, clarithromycin, and telithromycin).

2) Concomitant use of the following drugs is not recommended.

- Moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, and some macrolides).

3) Concomitant use of the following drugs requires caution.

- Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: Azithromycin and roxithromycin.

Ketoconazole/Erythromycin and QTc Prolongation: Separate *in vivo* pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these drugs (as both of these drugs significantly inhibit CYP3A4 enzyme). Both the C_{max} and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies. In these studies, concomitant use of domperidone and ketoconazole or erythromycin resulted in increase in QTc, over the observation period.

4.6Use in Special Populations

Pregnant Women

Esomeprazole: Pregnancy Category C; Domperidone: Pregnancy Category C. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to reproductive toxicity (embryonal/fetal development). Also, animal studies with the racemic mixture (i.e., omeprazole) do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity of esomeprazole.

There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses.

There are however, no adequate and well controlled studies available for use of esomeprazole with domperidone combination therapy during pregnancy. Thus, it is recommended that during pregnancy, S-RD Capsules should be used with caution and only if clearly needed.

Lactating Women

Esomeprazole is likely to present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that maternal doses of omeprazole 20 mg daily produce low levels in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants.

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

S-RD Capsules should not be used during breast feeding. Accordingly, a decision should be made whether to discontinue nursing or to discontinue/abstain from therapy, taking into account the benefit of the drug to the mother.

Paediatric Patients
Safety and efficacy of esomeprazole with domperidone combination therapy has not been established in paediatric patients. Thus, S-RD Capsules are not recommended for use in children.

Geriatric Patients
No overall differences in safety or effectiveness were observed between elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is generally necessary in the elderly patients.

Renal Impairment Patients
There is lack of data on use of esomeprazole in patients with severe renal insufficiency. On repeated administration, the elimination half-life of domperidone is prolonged in patients with severe renal impairment. S-RD Capsules can be administered in patients with mild to moderate renal dysfunction. In patients with severe renal impairment, S-RD Capsules should be used with caution and dose/dosage frequency may need to be reduced depending on the severity of the renal dysfunction.

Hepatic Impairment Patients
With esomeprazole, 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. With domperidone, no dosage adjustment is necessary in patients with mild hepatic impairment. Thus, S-RD Capsules can be administered in patients with mild hepatic dysfunction. However, S-RD Capsules are contraindicated in patients with moderate or severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines
Both, esomeprazole and domperidone have minor influence on the ability to drive and use machines. Adverse reactions such as dizziness and visual disturbances have been reported rarely with esomeprazole therapy. If affected, patients should not drive or use machines.

4.8Undesirable Effects
Esomeprazole
Clinical Trials Experience
The most frequently reported (≥ 1%) adverse reactions with esomeprazole were headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth.
Additional adverse reactions that were reported as possibly or probably related to esomeprazole with an incidence < 1% are as follows:
Body as a Whole: Enlarged abdomen, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like symptoms, generalized edema, leg edema, malaise, pain, rigors.
Cardiovascular: Flushing, hypertension, tachycardia.
Endocrine: Goiter.

Gastrointestinal (GI): Bowel irregularity, constipation aggravated, dyspepsia, dysphagia, GI dysplasia, epigastric pain, eructation, esophageal disorders, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorders, pharyngeal disorders, rectal disorders, increase in serum gastrin, tongue disorders, tongue edema, ulcerative stomatitis, vomiting.
Hearing: Earache, tinnitus.
Hematologic: Anemia, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia.
Hepatic: Abnormalities in hepatic function, including bilirubinemia, increase in AST (aspartate aminotransferase) and ALT (alanine aminotransferase).
Metabolic/Nutritional: Glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B_{12} deficiency, weight increase/decrease.
Musculoskeletal: Arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica.
Nervous System/Psychiatric: Anorexia, apathy, increased appetite, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect.
Reproductive: Dysmenorrhea, menstrual disorders, vaginitis.
Respiratory: Aggravated asthma, coughing, dyspnea, laryngeal edema, pharyngitis, rhinitis, sinusitis.
Skin and Appendages: Acne, angioedema, dermatitis, pruritus, rash, urticaria, sweating.
Special Senses: Otitis media, parosmia, taste loss, taste perversion.
Urogenital: Albuminuria, cystitis, dysuria, fungal infection, hematuria, frequent micturition, moniliasis, polyuria.
Visual: Conjunctivitis, abnormal vision.

Laboratory Abnormalities
The following clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole, were reported in $\leq$ 1% of patients: Increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone. Decreased levels of hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

Post-Marketing Experience
Acute kidney injury as an adverse drug reaction reported with the use of proton pump inhibitors. The following adverse reactions have been identified during post-marketing use of esomeprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Blood and Lymphatic: Agranulocytosis, pancytopenia.
Eye: Blurred vision.
Gastrointestinal: Pancreatitis, stomatitis, microscopic colitis.
Hepatobiliary: Hepatitis with or without jaundice, hepatic failure.

Immune System: Anaphylactic reaction/shock.
Infections and Infestations: GI candidiasis, *Clostridium difficile*-associated diarrhea.
Metabolism and Nutritional Disorders: Hypomagnesemia.
Musculoskeletal and Connective Tissue: Muscular weakness, myalgia, fractures.
Nervous System: Hepatic encephalopathy, taste disturbance.
Psychiatric: Aggression, agitation, depression, hallucination.
Renal and Urinary: Interstitial nephritis.
Reproductive System and Breast: Gynecomastia.
Respiratory, Thoracic, and Mediastinal: Bronchospasm.
Skin and Subcutaneous Tissue: Alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (sometime fatal), cutaneous lupus erythematosus.

Domperidone

Central Nervous System: As the pituitary gland is outside the blood-brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuro-endocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea. Extrapyramidal side effects are very rare in neonates and infants, and exceptional in adults. These side effects reverse spontaneously and completely as soon as the treatment is stopped. Other central nervous system-related effects of convulsion, agitation and somnolence also are very rare and primarily reported in infants and children.
The adverse drug reactions are ranked below by frequency, using the following convention: Very common (≥ 1/10), common (≥ 1/100 to <1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000), not known (cannot be estimated from available data).
General Disorders: Uncommon: Asthenia.
Immune System Disorder: Not known: Anaphylactic reactions including anaphylactic shock and angioedema.
Psychiatric Disorders: Uncommon: Anxiety, loss of libido; Not known: Agitation, nervousness.
Nervous System Disorders: Uncommon: Somnolence, headache; Not known: Extrapyramidal disorder, convulsions.
Eye Disorders: Not known: Oculogyric crisis.
Cardiac Disorders: Not known: Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, sudden cardiac death.
Gastrointestinal Disorders: Common: Dry mouth; Uncommon: Diarrhea.
Skin and Subcutaneous Tissue Disorders: Uncommon: Rash, pruritus; Not known: Urticaria, angioedema.
Reproductive System and Breast Disorders: Uncommon: Breast pain, breast tenderness, galactorrhoea; Not known: Gynaecomastia, amenorrhoea.
Renal and Urinary Disorders: Not known: Urinary retention.
Investigations: Not known: Abnormal liver function test, increased blood prolactin.

4.9Overdose

Esomeprazole

There is very limited experience with deliberate overdose of esomeprazole. The symptoms described in connection with deliberate overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Symptoms of esomeprazole overdose were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth.

No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not able to remove by dialysis. In the event of overdose, treatment should be symptomatic and supportive.

Domperidone

Symptoms of domperidone overdose may include agitation, altered consciousness, convulsions, disorientation, somnolence, and extrapyramidal reactions.

There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended. Anticholinergic, antiparkinson drugs may be helpful in controlling the extrapyramidal reactions.

5. Pharmacological Properties

5.1 Mechanism of Action

Esomeprazole

Esomeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid (hydrochloric acid - HCl) secretion by specific inhibition of the H+/K+-ATPase enzyme system at the secretory surface of the gastric parietal cell. Esomeprazole is a weak base and is concentrated and converted to the active form (i.e., the achiral sulphenamide) in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+K+-ATPase (the acid/proton pump), and inhibits both basal and stimulated acid secretion. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thereby reducing gastric acidity.

Domperidone

Domperidone is a dopamine receptor (D2) antagonist. Domperidone act predominantly on peripheral dopamine receptors and produces anti-emetic and gastrokinetic effects. Domperidone does not readily cross the blood-brain barrier (BBB). Thus, in domperidone users, especially in adults, extrapyramidal side effects are very rare (unlike metoclopramide). Anti-emetic effect of domperidone is due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors (D2) in the chemoreceptor trigger zone (CTZ), which lies outside the BBB in the area postrema.

Oral domperidone also increases lower esophageal sphincter (LES) pressure, thus, improve antroduodenal motility and accelerate gastric emptying.

5.2Pharmacodynamic Properties

Esomeprazole

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

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 5 days, mean peak acid output decreases by 90% when measured 6 to 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 76%, 54% and 24% for esomeprazole 20 mg. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Esomeprazole increases the mean fasting gastrin level in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Domperidone

Prokinetic Effect: The prokinetic (gastrokinetic) properties of domperidone are related to its peripheral dopamine receptor blocking action.

Antiemetic Effect: Domperidone produces antiemetic effect by blocking dopamine receptors (D2) peripherally. Inhibition of peripheral D2 receptor signaling prevents or relieves various GI symptoms, such as nausea and vomiting, and also relieves reflux and other symptoms associated with upper GI disorders.

5.3Pharmacokinetic Properties

Esomeprazole

Absorption: Like other PPIs, esomeprazole is an acid-labile drug and therefore, administered orally in the form of gastro-resistant pellets. Absorption of esomeprazole, therefore, begins only after the pellets leave the stomach. Esomeprazole is rapidly absorbed after oral administration. Onset of effect occurs within one hour after oral dosing with esomeprazole 20 mg and 40 mg. Peak plasma levels (C_{max}) occur approximately 1 to 2 hours (T_{max}) after oral dose. The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg.

Effect of Food: Food intake both delays and decreases the absorption of esomeprazole. Thus, esomeprazole should be administered at least one hour before meal.

Distribution: Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2 to 20 μmol/l. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 liters.

Metabolism: Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite.
Excretion: 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 with no tendency for accumulation during once-daily administration. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces. Less than 1% of parent drug is excreted in the urine.

Domperidone
Pharmacokinetics of domperidone in sustained release formulation is not available. Conventional formulation of domperidone (i.e., immediate release) has following pharmacokinetic properties:
Absorption: Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hour after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut and liver.
Effect of Food: Domperidone's bioavailability is enhanced in normal subjects when taken after a meal. The time of peak absorption is slightly delayed and the AUC somewhat increased when domperidone is taken after a meal.
Distribution: Oral domperidone does not appear to accumulate or induce its own metabolism. The peak plasma concentration (C_{max}) of 18 ng/ml to 21 ng/ml occurs 1.5 hours (T_{max}) after the oral dose. Domperidone is 91 to 93% bound to plasma proteins. Distribution studies with domperidone have shown wide tissue distribution, but low brain concentration.
Metabolism: Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.
Excretion: After oral dose, domperidone is excreted mainly by renal (31%) and biliary (66%) routes. The proportion of the drug excreted unchanged is small (10% of fecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7 to 9 hours in healthy subjects, but is prolonged in patients with severe renal insufficiency.

6. Nonclinical Properties

6.1 Animal Toxicology

Esomeprazole
Carcinogenicity: The carcinogenic potential of esomeprazole magnesium was assessed using studies of omeprazole, of which esomeprazole is an enantiomer. In two 24-month oral

carcinogenicity studies in rats, omeprazole at daily doses of 1.7 mg/kg/day, 3.4 mg/kg/day, 13.8 mg/kg/day, 44 mg/kg/day, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole.
In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.4 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group.
Mutagenesis: Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test.
Impairment of Fertility: The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.
Reproduction Studies: Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 42 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole.

Domperidone

Safety margins in *in vitro* proarrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- up to 45-fold. In *in vivo* models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4ng/ml, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day).
At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits. Development abnormalities observed in rats at a high exposure. Risk of carcinogenicity, mutagenicity or sensitisation cannot be excluded.

7. Description

S-RD Capsules are Light green / white coloured, Size 1, hard gelatin capsule containing white & orange colour pellets.

Each capsule of S-RD contains 40 mg of esomeprazole (in a gastro-resistant form) and 30 mg of domperidone (in a sustained release form) for oral administration in adults.

Esomeprazole Magnesium

Esomeprazole magnesium is the magnesium salt of esomeprazole, the S-isomer of omeprazole, with gastric proton pump inhibitor activity.

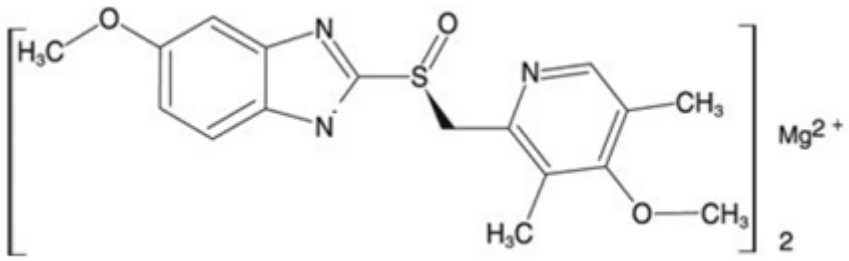
Esomeprazole magnesium salt is off-white to pale cream colored powder. It is slightly soluble in water.

Molecular Weight: 713.12 g/mol.

Molecular Formula: C34H36MgN6O6S2.

Chemical Name: 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2- pyridyl)methyl] sulfinyl]benzimidazole, magnesium salt (2:1).

Structural Formula:



Domperidone

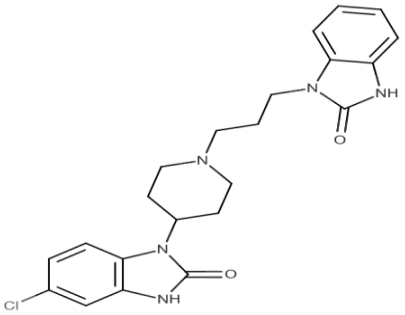
Domperidone is a dopamine receptor (D2) antagonist drug with antiemetic and gastrokinetic properties. Domperidone is white or almost white powder which is slightly soluble in water.

Molecular Weight: 425.9 g/mol.

Molecular Formula: C22H24ClN5O2.

Chemical Name: 6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2-one.

Structural Formula:



Inactive ingredients (excipients) of S-RD Capsules contain Hypromellose, Mannitol, Sucrose, Crospovidone, HPMC phthalate, Diethyl phthalate , Isopropyl alcohol, Dichloromethane, Polyvinyl Pyrrolidone K- 30, Talc, Ethyl cellulose, Colour Sunset Yellow Supra & Hard Gelatin Capsule Shell.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

15 capsules per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Instruct patients to take S-RD Capsules exactly as prescribed by doctor. Do not change the dose or stop therapy without consulting to your doctor.
- Instruct patients to swallow S-RD Capsules whole with water on empty stomach, preferably in the morning or at least 1 hour before meal. The capsules should not be opened, chewed or crushed.
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, do not take the missed dose. Take the next dose at your regular time. Do not take 2 capsules/doses at the same time to make up for the missed dose.
- Pregnant women can use this medicine only if essential and in consultation with their doctor.
- Advise nursing mothers to avoid use of this medicine during lactation or not to breastfeed their infants while on drug therapy.
- This medicine is not recommended for use in children.
- Instruct patients not to share this medication with other people even though symptoms are similar. It may harm them.
- Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. S-RD Capsules and certain other medicines can interact with each other causing serious side effects.

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Ranipur,
Haridwar – 249 403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 31/UA/2013, Date of Product Permission: 13/02/2019

12. Date of Revision

February 2023.

Marketed by:
EXCEL BLUE CROSS || EXCEL
Division of
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.