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

Rabeprazole (GR) and Domperidone (SR) Capsules
(Brand Name: R-RD® Capsules)

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:
Rabeprazole Sodium IP …… 20 mg
(as Gastro-resistant pellets)
Domperidone IP …… 30 mg
(as sustained release pellets)
Excipients ……..…… q.s.
Colours : Red Oxide of Iron & Sunset Yellow FCF.
Colours used in capsule shell : Brilliant Blue FCF, Erythrosine, Tartrazine, Sunset Yellow FCF. Titanium Dioxide IP.
Methylparaben and Propylparaben used as Antimicrobial preservatives.

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Rabeprazole 20 mg (in gastro-resistant form) with domperidone 30 mg (in sustained release form) per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

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

4.2Posology and Method of Administration

For oral administration in adults.
Recommended dose is 1 capsule to be administered once daily for 4 to 8 weeks.
R-RD Capsules may be administered with or without food. The capsules should be swallowed whole with water and not to be opened, chewed or crushed.
Or, as prescribed by the physician.

4.3Contraindications

R-RD Capsules are contraindicated in the following:

- Patients with known hypersensitivity to rabeprazole 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

Rabeprazole

Gastric Malignancy: In adults, symptomatic response to rabeprazole therapy does not preclude the presence of gastric malignancy; therefore the possibility of malignancy should be excluded prior to commencing treatment with rabeprazole. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a proton pump inhibitor (PPI).

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

Cyanocobalamin (Vitamin B_{12}) Deficiency: Daily treatment with acid-suppressing drugs over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with rabeprazole.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement as well as 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), monitoring of serum magnesium levels prior to initiation of PPI treatment and periodically thereafter should be considered.

Risk of Bone Fractures: 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 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 of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** Published observational studies suggest that PPI therapy like rabeprazole 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.

Subacute Cutaneous Lupus Erythematosus (SCLE): PPIs 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 rabeprazole therapy should be stopped immediately. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

Thrombocytopenia and Neutropenia: There have been post-marketing reports of blood dyscrasias (thrombocytopenia and neutropenia). In the majority of cases where an alternative etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole therapy.

Hepatic Effects: Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported in post-marketing studies. In the majority of cases where an alternative etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

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

Rabeprazole

Antiretroviral Drugs: The effect of PPI on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.

1) Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with rabeprazole may reduce antiviral effect and promote the development of drug resistance.
   - **Rilpivirine-Containing Products:** Concomitant use with rabeprazole is contraindicated.
   - **Atazanavir:** Co-administration of atazanavir 300 mg/ritonavir 10 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other PPIs. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.
   - **Nelfinavir:** Avoid concomitant use with rabeprazole.
2) Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with rabeprazole may increase toxicity. It is recommended to monitor for potential saquinavir toxicities.
3) There are other antiretroviral drugs which do not result in clinically relevant interactions with rabeprazole.

Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole, itraconazole): Rabeprazole produces a profound and long lasting inhibition of gastric acid secretion. An interaction with drugs whose absorption is pH dependent may occur. Rabeprazole can reduce the absorption/bioavailability of such drugs due to its effect on reduction of intragastric acidity.

- **Ketoconazole/Itraconazole:** Co-administration of rabeprazole with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. In healthy adult subjects, co-administration of rabeprazole 20 mg at steady state with a single 400 mg of ketoconazole resulted in approximately an average of 31% reduction in both C_{max} and AUC of ketoconazole. Therefore, individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole.
- **Mycophenolate Mofetil:** Co-administration of PPIs with mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant

patients receiving PPIs and mycophenolate mofetil. Use rabeprazole with caution in transplant patients receiving mycophenolate mofetil.

Antacids: In clinical trials, antacids were used concomitantly with the administration of rabeprazole and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed.

Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicity. A temporary withdrawal of rabeprazole therapy may be considered in some patients receiving high-dose of methotrexate.

Warfarin: Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased international normalized ratio (INR) and prothrombin time in patients receiving a PPI and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Thus, patients treated with rabeprazole and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Digoxin: When rabeprazole and digoxin are administered concomitantly, there is potential for increased exposure of digoxin. Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore, its clinical efficacy. Concomitant use of rabeprazole with clopidogrel should be discouraged or while using rabeprazole, consider an alternative antiplatelet therapy.

Tacrolimus: Potentially increased exposure of tacrolimus has been reported, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19; thus, monitoring of plasma levels of tacrolimus is advised. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentration.

Drug/Laboratory Tests Interactions

Increased Chromogranin A (CgA) Levels: Increased CgA level may interfere with investigations for neuroendocrine tumors. To avoid this interference, rabeprazole 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 PPI treatment.

Secretin Stimulation Test: Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma. Temporarily stop treatment with rabeprazole at least 14 days before assessing to allow gastrin levels to return to baseline.

False Positive Urine Tests for Tetrahydrocannabinol (THC): There have been reports of false positive urine screening tests for THC in patients receiving PPIs. An alternative confirmatory method should be considered to verify positive results.

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.

4.6 Use in Special Populations

Pregnant Women

Rabeprazole: Pregnancy Category C; Domperidone: Pregnancy Category C. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole, although low feto-placental transfer occurs in rats. No evidence of adverse developmental effects were seen in animal reproduction studies with rabeprazole administered during organogenesis at 13 and 8-times the human area under the plasma concentration-time curve (AUC) at the recommended dose for GERD, in rats and rabbits, respectively. There are no available human data on rabeprazole use in pregnant women.

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 rabeprazole with domperidone combination therapy during pregnancy. During pregnancy, R-RD Capsules should be used with caution and only if clearly needed.

Lactating Women

It is not known whether rabeprazole is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole is however excreted in rat mammary secretions.

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.

R-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 rabeprazole with domperidone combination therapy has not been established in paediatric patients. Thus, R-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

With rabeprazole, no dosage adjustment is necessary in patients with renal impairment. On repeated administration, the elimination half-life of domperidone is prolonged in patients with severe renal impairment. R-RD Capsules can be administered in patients with mild to moderate renal dysfunction. However, in patients with severe renal impairment, R-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

Administration of rabeprazole to patients with mild to moderate hepatic impairment resulted in increased exposure and decreased elimination; however, dosage adjustment of rabeprazole is not required. With domperidone, no dosage adjustment is necessary in patients with mild hepatic impairment. Thus, R-RD Capsules can be administered in patients with mild hepatic dysfunction. However, R-RD Capsules are contraindicated in patients with moderate or severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

Both, rabeprazole and domperidone have no or negligible influence on the ability to drive and use machines. However, adverse reactions such as dizziness and visual disturbances may occasionally occur with PPIs which may impair patient's mental alertness. If affected, patients should avoid driving a vehicle or operating machinery.

4.8Undesirable Effects

Rabeprazole

Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

In controlled clinical trials, the most commonly reported adverse reactions (≥ 2%) in patients treated with rabeprazole versus placebo include the following: Pain (3% vs. 1%), pharyngitis (3% vs. 2%), flatulence (3% vs. 1%), infection (2% vs. 1%), and constipation (2% vs. 1%).

Less common adverse reactions seen in controlled clinical trials (< 2% of patients treated with rabeprazole and greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: Headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, elevated hepatic enzymes, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

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-approval use of rabeprazole. 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 System Disorders: Agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia.

Ear and Labyrinth Disorders: Vertigo.

Eye Disorders: Blurred vision.

Hepatobiliary Disorders: Jaundice.

Immune System Disorders: Anaphylaxis, angioedema, systemic lupus erythematosus, Stevens-Johnson syndrome, toxic epidermal necrolysis (sometime fatal).

Infections and Infestations: *Clostridium difficile*-associated diarrhea.

Investigations: Increases in prothrombin time/INR (in patients treated with concomitant warfarin), elevations in thyroid stimulating hormone (TSH).
Metabolism and Nutrition Disorders: Hyperammonemia, hypomagnesemia.
Musculoskeletal System Disorders: Bone fracture, rhabdomyolysis.
Nervous System Disorders: Coma.
Psychiatric Disorders: Delirium, disorientation.
Renal and Urinary Disorders: Interstitial nephritis.
Respiratory, Thoracic and Mediastinal Disorders: Interstitial pneumonia.
Skin and Subcutaneous Tissue Disorders: Severe dermatologic reactions including bullous and other drug eruptions of the skin, cutaneous lupus erythematosus, erythema multiforme.

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

Rabeprazole

Experience with deliberate or accidental overdose with rabeprazole is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention.
No specific antidote is known. Rabeprazole is extensively protein bound and is, therefore, not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

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

Rabeprazole
Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole, proton-pump inhibitors - PPIs). As a weak base, rabeprazole is rapidly absorbed following oral dose and is concentrated in the acidic environment of the parietal cells. In gastric parietal cells (at pH 1.2), rabeprazole is converted to the active 'sulphenamide' form through 'protonation' and it subsequently reacts with the available cysteines on the proton pump.
Rabeprazole suppress gastric acid (hydrochloric acid – HCl) secretion by inhibiting the gastric H+/K+-ATPase enzyme at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

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

Rabeprazole

Oral administration of a 20 mg dose of rabeprazole provides rapid and effective reduction of gastric acid secretion. The onset of the antisecretory effect occurs within one hour, with the maximum effect occurring within 2 to 4 hours. Inhibition of basal and food-stimulated acid secretion 23 hours after the first dose of rabeprazole is 69% and 82% respectively, and the duration of inhibition lasts up to 48 hours. The duration of pharmacodynamic action of rabeprazole is much longer than its pharmacokinetic half-life (approximately one hour). This effect is probably due to the prolonged binding of rabeprazole to the parietal H+/K+-ATPase enzyme. The inhibitory effect of rabeprazole on acid secretion increases slightly with repeated once daily dosing, achieving steady state inhibition after 3 days. When the drug is discontinued, secretory activity normalizes over 2 to 3 days.

With once daily doses of rabeprazole 10 or 20 mg, serum gastrin levels increases in 2 to 8 weeks reflecting the inhibitory effects on acid secretion. Gastrin values returned to pretreatment levels, usually within 1 to 2 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

Rabeprazole

The pharmacokinetics (C_{max} and AUC) of rabeprazole are linear over the range of 10 mg to 40 mg. There is no significant accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing. Like other PPIs, rabeprazole is an acid-labile drug and therefore, administered orally in the form of gastro-resistant pellets. Absorption of rabeprazole therefore, begins only after the pellets leave the stomach.

Absorption: After oral administration of rabeprazole 20 mg, peak plasma concentrations (C_{max}) occur over a range of 2 to 5 hours (T_{max}). Absolute bioavailability for rabeprazole 20 mg (compared to intravenous administration) is approximately 52% (because of extensive pre-systemic metabolism). Additionally, the bioavailability does not appear to increase with repeat dose administration of rabeprazole.

Effect of Food: With rabeprazole, there was no clinically relevant interaction with food. Neither food nor the time of day of administration affects the absorption of rabeprazole. Thus, rabeprazole may be administered without regard to timing of meals.

Distribution: Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism: Rabeprazole is extensively metabolized. Rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome

P450 2C19 (CYP2C19) to desmethyl rabeprazole. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. A significant portion of rabeprazole is also metabolized via systemic non-enzymatic reduction to a thioether compound.

Excretion: Following a single 20 mg oral dose of rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid, glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. No unchanged rabeprazole was recovered in the urine or feces. In healthy subjects, the plasma half-life is approximately one hour (range 0.7 to 1.5 hours) and the total body clearance is estimated to be 283 ± 98 ml/min.

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

Rabeprazole

Carcinogenesis: In an 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μg•hr/ml which is

1.6 times the human exposure (plasma $AUC_{0-\infty}$ = 0.88 μg•hr/ml) at the recommended dose for GERD (20 mg/day).
In a 28-week carcinogenicity study in p53+/- transgenic mice, rabeprazole at oral doses of 20, 60, and 200 mg/kg/day did not cause an increase in the incidence rates of tumors but produced gastric mucosal hyperplasia at all doses. The systemic exposure to rabeprazole at 200 mg/kg/day is about 17 to 24 times the human exposure at the recommended dose for GERD.
In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60, and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 μg•hr/ml which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 μg•hr/ml (0.2 times the human exposure at the recommended dose for GERD).
Mutagenesis: Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test, and the mouse lymphoma cell forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.
Impairment of Fertility: Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μg•hr/ml, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.
Developmental Toxicity: Embryo-fetal developmental studies have been performed in rats during organogenesis at intravenous doses of rabeprazole up to 50 mg/kg/day (plasma AUC of 11.8 μg•hr/ml, about 13 times the human exposure at the recommended oral dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μg•hr/ml, about 8 times the human exposure at the recommended oral dose for GERD) and have revealed no evidence of harm to the fetus due to rabeprazole.

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

R-RD Capsules are Dark Green & light yellow coloured hard gelatin capsules of size "1" containing red & orange colour pellets.

Each capsule of R-RD contains 20 mg of rabeprazole (in a gastro-resistant form) and 30 mg of domperidone (in a sustained release form) for oral administration in adults.

Rabeprazole Sodium

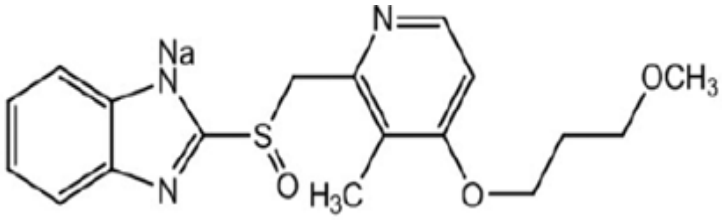
Rabeprazole sodium is a substituted benzimidazole, proton pump inhibitor (PPI) class of antisecretory agents. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform, and ethyl acetate and insoluble in ether and n-hexane.

Molecular Weight: 381.42 g/mol.

Molecular Formula: C18H20N3NaO3S

Chemical Name: 2-[[[4-(3methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt..

Structural Formula:



Domperidone

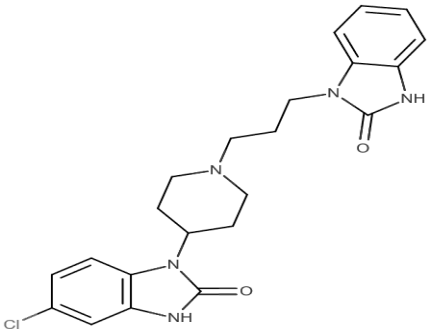
Domperidone is a dopamine receptor (D2) antagonist drug with antiemetic and gastrokinetic properties. Domperidone is white or almost white powder which is slightly soluble in water.

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 R-RD Capsules contain Hypromellose, Mannitol, Sucrose, Crospovidone, HPMC phthalate, Diethyl phthalate , Colour Iron Oxide Red, 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 R-RD Capsules exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Instruct patients to swallow R-RD Capsules as a whole with water and not to open, chew or crush the capsules.
- 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. R-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.
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