For the use of a Registered Medical Practitioner only

℞ Rabeprazole & Sustained Release Domperidone Capsules

Rabiet DSR*

COMPOSITION:

Each hard gelatin capsule contains :

Rabeprazole Sodium IP..... 20 mg
(as enteric coated pellets)

Domperidone IP..... 30 mg
(as sustained release pellets)

Excipients..... q.s.

Colours: Lake of Red Oxide of Iron & Lake of Sunset Yellow FCF

Approved colours used in capsule shells.

PHARMACEUTICAL FORM

Hard Gelatin Capsule.

THERAPEUTIC INDICATION

Indicated for the treatment of adult patients with gastroesophagal reflux disease (GERD).

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage is 1 capsule once daily or as directed by the Physician. Method of administration: For oral use only.

This hard gelatin capsule should be swallowed whole with liquid and should not be chewed or crushed.

CONTRAINDICATIONS

Contraindicated in patients with a known hypersensitivity to the any of the active substance or to any excipients. Rabeprazole is contraindicated in pregnancy & lactation. Rabeprazole is contraindicated in pregnancy & lactation. Domperidone contraindicated in:

Prolactin-releasing pituitary tumour (prolactinoma).

When stimulation of the gastric motility could be harmful e.g in the patients with gastro-intestinal haemorrhage, mechanical obstruction or perforation.

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 or underlying cardiac diseases such as congestive heart failure. Co-administration with QT-prolonging drugs, at the exception of apomorphine.

Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Rabeprazole

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabeprazole. Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance. A risk of cross-hypersensitivity reactions with other proton pump inhibitor or substituted benzimidazoles cannot be excluded.

No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However because there are no clinical data on the use of rabeprazole in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole is first initiated in such patients.

Treatment with proton pump inhibitors, including rabeprazole, may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and Clostridium difficile.

Co-administration of atazanavir with rabeprazole is not recommended.

Paediatric population: Rabeprazole is not recommended for use in the children due to a lack of data on safety and efficacy. There have been post marketing reports of the blood dyscrasias (thrombocytopenia and neutropenia). In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole. Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since market authorisation. In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

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 Rabeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 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.

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), 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 the established treatment guidelines. Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false-positive results in diagnostic investigations for neuroendocrine tumors. Providers should temporarily stop rabeprazole treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high.

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking rabeprazole and may occur at any point during rabeprazole therapy. Acute tubulointerstitial nephritis can progress to renal failure. Rabeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Concomitant use of rabeprazole with methotrexate

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

Influence on vitamin B12 absorption

Rabeprazole sodium, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo-or a-chlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Domperidone

Renal Impairment: The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

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.

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 patient with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section 4.3). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Domperidone should be used at the lowest effective dose in adults and children.

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

Use in infants: Neurological side effects are rare (see "Undesirable effects" section). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

DRUG INTERACTION

Rabeprazole

Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur.

Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. 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.

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.

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 proton pump inhibitors. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.

Domperidone

Concomitant administration of anticholinergic drugs may antagonize the anti-dyspeptic effect of domperidone.

The main metabolic pathway of domperidone is through CYP3A4. Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided.

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.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions. Concomitant use of the following substances is contraindicated

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 (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone) (see section 4.3).
- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled.

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e:

- protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin and telithromycin) Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides. Concomitant use of the following substances requires caution in use

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

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.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies. In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while Ketoconazole monotherapy (200mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

USE IN SPECIAL POPULATION

Pregnancy

There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole is contraindicated during pregnancy.

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

Breastfeeding

It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore Rabeprazole must not be used during breast feeding.

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

Paediatric population

Rabeprazole, not recommended for use in children due to a lack of data on safety and efficacy.

Due to the need for accurate dosing, Domperidone tablets are unsuitable for use in children and adolescents weighing less than 35 kg.

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

Renal Impairment

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

Hepatic Impairment

Since domperidone is highly metabolized in the liver, this Capsule should be not be used in patients with hepatic impairment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rabeprazole would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

Domperidone has no or negligible influence on the ability to drive or use machines.

UNDESIRABLE EFFECTS

Rabeprazole

Proton Pump Inhibitors associated Acute Kidney Injury: Acute kidney injury has been reported with the use of proton pump inhibitors (PPIs) including Pantoprazole, omeprazole, lansoprazole, esomeprazole, and Rabeprazole etc.

The most commonly reported adverse drug reactions, during controlled clinical trials with Rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience.

Frequencies are defined as: common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Infection				
Blood and lymphatic system disorders			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity[1,2]		
Metabolism and nutrition disorders			Anorexia		Hyponatremia Hypomagnesaemia
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous system disorders	Headache Dizziness	Somnolence			
Eye disorders			Visual disturbance		
Vascular disorders					Peripheral oedema
Respiratory, thoracic and mediastinal disorders	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic gland polyps (benign)	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		Microscopic colitis
Hepatobiliary disorders			Hepatitis Jaundice Hepatic encephalopathy[3]		
Skin and subcutaneous tissue disorders		Rash Erythema[2]	Pruritus Sweating Bullous reactions[2]	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip,wrist or spine[4]			
Renal and urinary disorders		Urinary tract infection	Tubulointerstitial nephritis (with possible progression to renal failure)		
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic enzymes[3]	Weight increased		

1 Includes facial swelling, hypotension and dyspnoea

2 Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.

3 Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Rabeprazole 10mg Gastro-resistant Tablets is first initiated in such patients.

Domperidone

Tabulated list of adverse reactions

The safety of Domperidone was evaluated in clinical trials and in postmarketing experience. The clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GORD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo-controlled studies. All patients were at least 15 years old and received at least one dose of domperidone (domperidone base). The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism were excluded.

The following frequencies are applied:

Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), Where frequency cannot be estimated from clinical trials data, it is recorded as "Not known".

System Organ Class	Adverse Drug Reaction Frequency		
	Common	Uncommon	Not known
Immune system disorder			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety	Agitation Nervousness
Nervous system disorders		Somnolence Headache	Convulsion Extrapyramidal disorder
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias Sudden cardiac death QTc prolongation Torsade de Pointes
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorder		Rash Pruritus	Urticarial
Angioedema			
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhoea Breast pain Breast tenderness	Gynaecomastia Amenorrhoea
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal Blood prolactin increased

In 45 studies where Domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

OVERDOSE

Rabeprazole

Experience to date with deliberate or accidental overdose 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 sodium is extensively protein bound and is, therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Domperidone

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsion, 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. Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, Proton pump inhibitor, and Dopamine antagonist.

Rabeprazole, is a selective and irreversible proton pump inhibitor, suppresses gastric acid secretion by specific inhibition of the H+, K+-ATPase, which is found at the secretory surface of parietal cells. In doing so, it inhibits the final transport of hydrogen ions (via exchange with potassium ions) into the gastric lumen. Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-

ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

Domperidone, is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extra-pyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of central dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. Studies in humans have shown oral domperidone to increase lower esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

Pharmacokinetic properties

Absorption

Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism.

In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone`s bioavailability is enhanced in normal subjects when taken after a meal, patients with gastrointestinal complaints should take domperidone 15 to 30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone.

Distribution

Rabeprazole is approximately 97% bound to human plasma proteins.

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21ng/ml after 2 weeks of oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91% to 93% bound to plasma proteins.

Metabolism

Rabeprazole sodium, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4).

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 CYP450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Following a single 20 mg 14C labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.

Urinary and fecal excretions amount to 31% and 66% of the oral domperidone dose, respectively. 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 impairment.

INCOMPATIBILITY

Not applicable.

STORAGE INSTRUCTIONS

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

Keep all medicines out of reach of children.

Capsule should be swallowed whole and not to be opened, chewed or crushed.

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