For the use of a Registered Medical Practitioner only

℞ Rabeprazole and Domperidone Tablets

Rabiet D*

1. GENERIC NAME

Rabeprazole and Domperidone Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains:

Rabeprazole Sodium IP ..... 20 mg

Domperidone Maleate IP

eq. to Domperidone ..... 10 mg

Colours: Yellow Oxide of Iron & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Rabeprazole 20mg, Domperidone 10mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of adult patients with gastroesophageal reflux disease (GERD)

4.2 Posology and method of administration

Posology

The recommended adult dosage is 1 tablet once daily or as directed by the Physician.

Method of administration: For oral use only.

Patients should be instructed or advised to swallow the tablet whole at least 1 hour before meals with some water and must not be opened, chewed or crushed.

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity to the active substance Rabeprazole, to substituted benzimidazoles or domperidone or any other component of this product. PPIs, including Rabeprazole, are contraindicated with rilpivirine-containing products.

Domperidone is contraindicated in the following situations:

- 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 the QT-prolonging drugs, at the exception of apomorphine; and co-administration with potent CY3A4 inhibitors (regardless of their QT prolonging effects).
- Prolactin-releasing pituitary tumour (prolactinoma); and renal impairment.

Domperidone should not be used when stimulation of gastric motility could be harmful: gastro-intestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use Rabeprazole

Presence of Gastric Malignancy

Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI.

Interaction with Warfarin

Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including rabeprazole sodium. Discontinue rabeprazole sodium if acute interstitial nephritis develops.

Clostridium difficile-Associated Diarrhoea

Published observational studies suggest that PPI therapy like rabeprazole sodium may be associated with an increased risk of Clostridium difficile-associated diarrhoea, especially in hospitalized patients.

This diagnosis should be considered for diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture

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.

Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including rabeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving rabeprazole sodium, discontinue the drug and refer the patient to the appropriate specialist for evaluation.

Cyanocobalamin (Vitamin B-12) Deficiency

Long term therapy with any acid-suppressing medications (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with rabeprazole sodium.

Hypomagnesemia

Hypomagnesemia has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. 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., diuret- ics), monitoring magnesium levels prior to initiation of PPI treatment and periodically is advised.

Interaction with Methotrexate

Concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may increase and prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In some patients, during high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered.

Fundic Gland Polyps

An increased risk of fundic gland polyps has been associated with long-term use of PPIs, especially beyond one year. On most occasions, these fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Domperidone

Prolactin levels

There are limited safety data in long-term use (i.e. beyond six months) of Domperidone. However, it has been shown to produce an increase in plasma prolactin. The raised level persists with chronic administration but falls to normal on discontinuing the drug. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of Domperidone is contemplated in a patient with a past history of breast cancer.

Endocrine disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with drugs which stimulate prolactin release. The clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of Domperidone and other prolactin stimulating drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis.

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 should be used at the lowest effective dose in adults and children. 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. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the pro-arrhythmic risk.

Use in infants

Neurological side effects are rare. Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children.

Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

Use with apomorphine

Domperidone is contraindicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks; and only if the recommended precau- tions for co-administration. Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patient should consult their physician. Patient should be advised to promptly report any cardiac symptoms.

4.5 Drugs interactions

Rabeprazole

Drugs Metabolized by CYP450

Rabeprazole is metabolized by the CYP450 drug-metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system.

Warfarin

There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in the INR and prothrombin time may lead to abnormal bleeding and even death.

Cyclosporine

Rabeprazole inhibits cyclosporine metabolism with an IC50 of 62 micromolar, a concentration that is over 50 times higher than the Cmax in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole.

Compounds Dependent on Gastric pH for Absorption

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds that are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg q.d. resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and Cmax for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Coadministration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations. Concomitant use of atazanavir and PPIs is not recommended. Co-administration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Drugs Metabolized by CYP2C19

Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.

Combined Administration with Clarithromycin

Combined administration consisting of rabeprazole, amoxicillin, and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclarithromycin. Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs.

Methotrexate

Concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Clopidogrel

Concomitant administration of rabeprazole and clopidogrel in healthy subjects had no clinically meaningful effect on exposure to the active metabolite of clopidogrel. No dose adjustment of clopidogrel is necessary when administered with an approved dose of rabeprazole sodium.

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.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions

Concomitant use of the following substances is contraindicated:

Examples of QTc-prolonging medicines include:

- Anti arrhythmics class IA (e.g. disopyramide); • anti arrhythmics class III (e.g. amiodarone*, dronedarone, sotalol) • some antipsychotics (e.g. haloperidol) • some antidepressants (e.g. citalopram, escitalopram) • some antibiotics (e.g. erythromycin*, clarithromycin*, levofloxacin, moxifloxacin) • some antifungal agents (e.g. pentamidine) • some antimalarial agents (e.g. lumefantrine) • some azole antifungals, (e.g. itraconazole*, ketoconazole*, voriconazole*,fluconazole*) • some calcium antagonists, (e.g. diltiazem*, verapamil*) • some gastrointestinal agents (e.g. prucalopride, granisetron, ondansetron) • certain HIV protease inhibitors (e.g. atazanavir*, fosamprenavir*, indinavir*, ritonavir*, saquinavir*) • some antineoplastic agents (e.g. toremifene, vandetanib) • others (e.g. aprepitant* and methadone).

Concurrent use of domperidone with medicines that are potent inhibitors of CYP3A4 is contraindicated due to an increased risk of sudden cardiac death shown in postmarket studies:

Examples of potent CYP3A4 inhibitors include:

- Azole antifungals, such as fluconazole, itraconazole, ketoconazole and voriconazole.
- Macrolide antibiotics, such as clarithromycin and erythromycin;
- HIV protease inhibitors, such as amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir and saquinavir;
- Calcium antagonists, such as diltiazem and verapamil • Amiodarone; • Aprepitant; • Telithromycin • Nefazodone.

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 contrain- dicated 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 medi- ated 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 indi- vidual 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.

Miscellaneous Interactions:

Antacids or antisecretory drugs should not be taken simultaneously with domperidone, since they reduce its oral bioavailability (i.e., they should be taken after meals and not before meals). Dosing with these agents should be separated from dosing with domperidone by at least 2 hours.

4.6 Use in specific populations

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

Due to the need for accurate dosing, Domperidone is unsuitable for use in children & adolescents weighing <35kg.

Renal Impairment

Rabeprazole/Domperidone tablets 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 Tablet should be not be used in patients with hepatic impairment.

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rabeprazole Gastro-resistant Tablets 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.

4.8 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 esomeprazole, omeprazole, pantoprazole, lansoprazole, 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: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data):

Infections and infestations: Common: Infection.

Blood and lymphatic system disorders: Rare: Neutropenia, Leucopenia, Thrombocytopenia, Leucocytosis.

Immune system disorders: Rare: Hypersensitivity[1,2].

Metabolism and nutrition disorders: Rare: Anorexia. Not known: Hyponatremia and Hypomagnesaemia[4].

Psychiatric disorders: Common: Insomnia. Uncommon: Nervousness. Rare: Depression. Not known: Confusion.

Nervous system disorders: Common: Headache, Dizziness. Uncommon: Somnolence.

Eye disorders: Rare: Visual disturbance.

Vascular disorders: Not known: Peripheral oedema.

Respiratory, thoracic and mediastinal disorders: Common: Cough, Pharyngitis, and Rhinitis. Uncommon: Bronchitis, Sinusitis.

Gastrointestinal disorders: Common: Diarrhoea, vomiting, nausea, abdominal pain, constipation, flatulence, fundic gland polyps (benign). Uncommon: Dyspepsia, dry mouth and eructation. Rare: Gastritis, stomatitis, and taste disturbance. Not known: Microscopic colitis.

Hepatobiliary disorders: Rare: Hepatitis, Jaundice and Hepatic encephalopathy[3].

Skin and subcutaneous tissue disorders: Uncommon: Rash, Erythema2. Rare: Pruritus, Sweating and Bullous reactions[2]. Very rare: Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens- Johnson syndrome (SJS). Not known: Subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders: Common: Non-specific pain, Back pain. Uncommon: Myalgia, Leg cramps, Arthralgia, and Fracture of the hip, wrist or spine.

Renal and urinary disorders: Uncommon: Urinary tract infection. Rare: Interstitial nephritis.

Reproductive system and breast disorders: Not known: Gynecomastia.

General disorders and administration site conditions: Common: Asthenia, Influenza like illness. Uncommon: Chest pain, Chills, and Pyrexia.

Investigations: Uncommon: Increased hepatic enzymes[3]. Rare: 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 is first initiated in such patients

[4] See Special warnings and precautions for use

Proton pump inhibitor use was found to be associated with increased risks for acute kidney injury and chronic kidney disease.

Postmarketing Experience

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: sudden death; coma, hyperammonemia; jaundice; rhabdomyolysis; disorientation and delirium; anaphylaxis; angioedema; bullous and other drug eruptions of the skin; severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; interstitial pneumonia; interstitial nephritis; TSH elevations; bone fractures; hypomagnesemia and Clostridium difficile associated diarrhoea. In addition, agranulocytosis, hemolytic anaemia, leukopenia, pancytopenia, and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported.

Domperidone

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 domperi- done (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 used for the description of the occurrence of adverse reactions: 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".

Immune system disorder: Not known: Anaphylactic reaction (including anaphylactic shock).

Psychiatric disorders: Uncommon: Loss of libido, anxiety. Not known: Agitation, nervousness.

Nervous system disorders: Uncommon: Somnolence, headache. Not known: Convulsion, extrapyramidal disorder.

Eye disorders: Not known: Oculogyric crisis.

Cardiac disorders: Not known: Ventricular arrhythmias, sudden cardia death, QTc prolongation, and Torsade de Pointes.

Gastrointestinal disorders: Common: Dry mouth. Uncommon: Diarrhoea.

Skin and subcutaneous tissue disorder: Uncommon: Rash, pruritus. Not known: Urticarial, angioedema.

Renal and urinary disorders: Not known: Urinary retention.

Reproductive system and breast disorders: Uncommon: Galactorrhoea, breast pain, breast tenderness. Not known: Gynaecomastia, and amenorrhoea.

General disorders and administration site conditions: Uncommon: Asthenia.

Investigations: Not known: 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

4.9 Overdose

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60mg twice daily, or 160mg once daily. Effects are generally minimal, repre- sentative 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 utilized.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Rabeprazole

Rabeprazole 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

Domperidone is a dopamine antagonist with anti-emetic properties domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal 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 dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2 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 is metabolized 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 labeled oral dose of rabeprazole, 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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Rabeprazole

Studies in neonatal/juvenile and young adult rats and dogs were performed. In juvenile animal studies rabeprazole sodium was administered orally to rats for up to 5 weeks and to dogs for up to 13 weeks, each commencing on Day 7 post-partum and followed by a 13-week recovery period. Rats were dosed at 5, 25 or 150 mg/kg/day and dogs were dosed at 3, 10 or 30 mg/kg/day. The data from these studies were comparable to those reported for young adult animals. Pharmacologically mediated changes, including increased serum gastrin levels and stomach changes, were observed at all dose levels in both rats and dogs. These observations were reversible over the 13-week recovery periods. Although body weights and/or crownrump lengths were minimally decreased during dosing, no effects on the development parameters were noted in either juvenile rats or dogs.

Domperidone

Animal Toxicology or Pharmacology

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes exposure ratios ranged between 26 – 47-fold, based on IC50 values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg administered 3 times a day. safety margins for prolongation of action potential duration in in vitro experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 45-fold.

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 concentra- tions 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). The relevance of the latter study for humans following exposure to rally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3- fold. 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.

7. DESCRIPTION

The active ingredients in this product are: Rabeprazole and Domperidone. It is indicated for the treatment of adult patients with gastroesophageal reflux disease (GERD) not responding to Rabeprazole

alone or should be used as directed by the Physician.

Rabeprazole sodium, which is a proton pump inhibitor (PPI). It is a substituted benzimidazole known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt. It has an empirical formula of C18H20N3NaO3S and a molecular weight of 381.42.

Domperidone is a dopamine antagonist with anti-emetic properties. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mecha- nisms. The molecular formula of domperidone is C22H24ClN5O2 and molecular weight 425.9 g/mol.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

24 Months

8.3 Packaging information

Blister of 10 Tablets

8.4 Storage and handing instructions

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

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

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

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

What is Rabeprazole and Domperidone tablet and it is used for?

It is combination of two medicines, Rabeprazole and Domperidone; which is indicated for the treatment of adult patients with gastroesophageal reflux disease (GERD). Rabeprazole belong to a group of medicines called Proton Pump Inhibitors (PPIs). Rabeprazole act by reducing the amount of acid made by the stomach. Domperidone belongs to a group of medicines called 'dopamine antagonists'. You should take these tablets exactly as prescribed, at the lowest dose possible and for the shortest time needed.

Do not take if you have an allergy to the drug

Do not take this medicine if you:

- are allergic to Rabeprazole, domperidone or any of the other ingredients of this medicine.

Before you take this drug, tell your healthcare practitioner about other medications you may be taking Rabeprazole may interact with Antifungals, Atazanavir, Methotrexate.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important in case you are taking any of the following medicines:

Before you use Domperidone and apomorphine, your doctor will ensure that you tolerate both medicines when used simultaneously. Ask your doctor or specialist for a personalised advice. Please refer to apomorphine leaflet.

Tell your doctor or pharmacist if you are taking drugs to treat infection, heart problems or AIDS/HIV. It is important to ask your doctor or pharmacist if Domperidone is safe for you when you are taking any other medicines, including medicines obtained without prescription.

Warnings and precautions

Do not take Rabeprazole/Domperidone Tablets if you

- are pregnant or breast-feeding.

Talk to your doctor or pharmacist before taking Domperidone if you're pregnant, might become pregnant or think you may be pregnant. If you're breast-feeding. It is best not to take Domperidone if you are breastfeeding. This is because small amount of Domperidone have been detected in breast milk. Domperidone may cause unwanted side effects affecting the heart in a breast-fed baby. Domperidone should be used during breast feeding only if your physician considers this clearly necessary. Ask your doctor for advice before taking this medicine.

Driving and using machines

It is unlikely that Rabeprazole would affect your ability to drive or operate machinery. However, it can cause sleepiness. Therefore, driving and operating complex machinery should be avoided if you are affected.

You may feel sleepy, confused or have less control over your movements while taking Domperidone. If this happens, do not drive or use any tools or machines.

How should you take this medicine?

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is: One tablet once daily or as directed by the Physician.

Method of administration: For oral use only.

Patients should be instructed or advised to swallow the tablet whole at least 1 hour before meals with some water and must not be opened, chewed or crushed.

If you take more this medicine than you should:

If you have taken more this medicine than prescribed by your doctor, seek medical advice.

If you forget to take this medicine:

Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then.

What are the possible side effects of these tablets?

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you notice any of the following serious side effects, stop taking this medicine and contact a doctor immediately.

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, Esome- prazole, Rabeprazole etc.

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole sodium were headache, diarrhoea, flatulence, constipation, fundic gland polyps (benign), abdomi- nal pain, dizziness, asthenia, insomnia, cough, pharyngitis, rhinitis, non-specific pain, back pain, and rashes. Hypersensitivity includes facial swelling; hypotension and dyspnoea have been reported.

Like all medicines, Domperidone can have side effects, although not everybody gets them. Uncommon (may affect up to 1 in 100 people):

- Involuntary movements of the face or arms and legs, excessive trembling, excessive muscle stiffness or muscle spasm Not known (frequency cannot be estimated from the available data):
- Seizures
- A type of reaction that may occur soon after administration and is recognised by skin rash, itching, shortness of breath, and/or a swollen face
- A severe hypersensitivity reaction that may occur soon after administration that is characterised by hives, itching, flushing, fainting, and difficulty breathing among other possible symptoms
- Disorders of the cardiovascular system: heart rhythm disorders (rapid or irregular heart beat) have been reported; if this happens, you should stop the treatment immediately.

Domperidone may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old or taking doses higher than 30 mg per day.

Domperidone should be used at the lowest effective dose.

Some patients who have used Domperidone for conditions and dosages requiring medical oversight have experienced the following unwanted effects: Restlessness; swollen or enlarged breasts, unusual discharge from breasts, irregular menstrual periods in women, difficulty breastfeeding, depression, and hypersensitivity.

Stop treatment with Rabeprazole & Domperidone Tablets and contact your doctor immediately (in bold) if you experience any of the unwanted events as described above.

How should I store this medicine?

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

Keep out of reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

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Note: This prescribing information is applicable for India Market only