RABICIP D Capsules (Rabeprazole sodium + Domperidone)

Quantitative and Qualitative Composition

Each Hard Gelatin Capsule Contains

Rabeprazole Sodium IP …20mg

(As enteric coated pellets)

Domperidone IP……30mg

(As sustained release pellets)

Colours: Ferric Oxide (Red) USP.NF, Brilliant

Blue Lake and Titanium Dioxide I.P

Approved Colour used in capsule shell

Dosage Form and Strength

Enteric coated Rabeprazole Sodium 20mg and Domperidone Sustained Release 30mg Oral Capsule

Clinical Particulars

Therapeutic Indication

For the treatment of Gastro-Esophageal Reflux Disease (GERD) not responding to Rabeprazole alone

Posology and Method of Administration

One capsule once daily

Contraindications

Rabeprazole

- Hypersensitivity to the active substance or to any of the excipients listed in section
- Pregnancy
- Breast feeding

Domperidone

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 QT-prolonging drugs, at the exception of apomorphine

• Co-administration with potent CY3A4 inhibitors (regardless of their QT prolonging effects)

• Known hypersensitivity to domperidone or any of the excipients.

• Prolactin-releasing pituitary tumour (prolactinoma)

• Renal impairment

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

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.

Patients should be cautioned that this medicine should not be chewed or crushed but should be swallowed whole.

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

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.

Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since market authorization. In the majority of cases where an alternative etiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

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 20mg is first initiated in such patients.

Co-administration of atazanavir with rabeprazole is not recommended.

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

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

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

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

Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors.

Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

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.

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.

Increased Chromogranin A (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 proton pump inhibitor treatment.

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 rabeprazole and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

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

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; *see methotrexate prescribing information*) may elevate and prolong serum concentrations 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.

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed 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

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

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.

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-prolonging drugs or CYP3A4 inhibitors.

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 proarrythmic risk.

Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration mentioned in the apomorphine.

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.

Drug Interactions

Rabeprazole

Clinically Relevant Interactions Affecting Drugs Co-Administered with Rabeprazole Sodium and Interactions with Diagnostics:

Antiretrovirals	
Clinical Impact:	The effect of PPI on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • 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. • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with rabeprazole may increase toxicity. • There are other antiretroviral drugs which do not result in clinically relevant interactions with rabeprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with rabeprazole sodium is contraindicated Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with rabeprazole sodium. See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. Other antiretrovirals: See prescribing information.
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death
Intervention:	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.
Methotrexate	
Clinical Impact:	Concomitant use of rabeprazole with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of methotrexate with PPIs have been conducted
Intervention:	A temporary withdrawal of rabeprazole sodium may be considered in some patients receiving high dose methotrexate administration.

Digoxin	
Clinical Impact:	Potential for increased exposure of digoxin.
Intervention:	Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations. See prescribing information for digoxin.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole, itraconazole)	
Clinical Impact:	Rabeprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	Mycophenolate mofetil (MMF): Co-administration of PPIs in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving rabeprazole sodium and MMF. Use rabeprazole sodium with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.
Combination Therapy with Clarithromycin and Amoxicillin	
Clinical Impact:	Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and are contraindicated.
Intervention:	See *Contraindications* and *Warnings and Precautions* in prescribing information for clarithromycin.
Tacrolimus	
Clinical Impact:	Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Intervention:	Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.
Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	Serum chromogranin A (CgA) levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors.
Intervention:	Temporarily stop rabeprazole sodium treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
Interaction with Secretin Stimulation Test	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
Intervention:	Temporarily stop treatment with rabeprazole sodium at least 14 days before assessing to allow gastrin levels to return to baseline.

False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
Intervention:	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.

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 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. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore, domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Lactation

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.

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. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women. Caution should be exercised in case of QTc prolongation risk factor in breast-fed infants.

Paediatric Use

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

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

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)

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[4]
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			
Renal and urinary disorders		Urinary tract infection	Interstitial nephritis		
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 dyspnea

[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.

Domperidone

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 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”.

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 (see section 4.4)			Ventricular arrhythmias Sudden cardia 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

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

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.

Symptoms

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

Pharmacological Properties

Mechanism of Action

Rabeprazole

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 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. 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 esophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion

Pharmacodynamic Properties

Rabeprazole

Anti-secretory activity: After oral administration of a 20 mg dose of rabeprazole sodium the onset of the anti-secretory effect occurs within one hour, with the maximum effect occurring within two to four hours. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of rabeprazole sodium are 69 % and 82 % respectively and the duration of inhibition lasts up to 48 hours. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalises over 2 to 3 days.

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

Serum gastrin effects: In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium, for up to 43 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion and remained stable while treatment was continued. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving rabeprazole or comparator treatment for up to 8 weeks have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of *H. pylori* infection. In over 250 patients followed for 36 months of continuous therapy, no

significant change in findings present at baseline was observed.

Other effects: Systemic effects of rabeprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20 mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, oestrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone or somatotrophic hormone.

Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with amoxicillin. Rabeprazole does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal *H. pylori* infection.

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. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. 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.

In accordance with ICH-E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline_of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90% CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effect were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day). The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5msec (95 % CI: 0.6 to 14.4), respectively.

Clinical study in infants and children 12 years of age and younger

A multicentre, double-blind, randomised, placebo-controlled, parallel-group, prospective study was conducted to evaluate the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged 6 months to 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), randomised subjects received domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone/day), or placebo, 3 times a day, for up to 7 days. This study did not achieve the primary objective, which was to demonstrate that domperidone suspension plus ORT is more effective than placebo plus ORT at reducing vomiting episodes during the first 48 hours after the first treatment administration.

Pharmacokinetic Properties

Rabeprazole

Rabeprazole is an enteric-coated pellet formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the pellet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) 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. Additionally the bioavailability does not appear to increase with repeat administration. 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. There was no clinically relevant interaction with food. Neither food nor the time of day of administration of the treatment affect the absorption of rabeprazole sodium.

Rabeprazole is approximately 97 % bound to human plasma proteins.

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). In these studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although *in vitro* studies may not always be predictive of *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.

Following a single 20 mg ^{14}C 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.

Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rabeprazole.

In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤5 ml/min/1.73 m^2), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the C_{max} in these patients was about 35 % lower than the corresponding parameters in healthy volunteers. The mean half-life of rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy volunteers.

Following a single 20 mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3-fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the C_{max} to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.

Elimination of rabeprazole was somewhat decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled, the C_{max} increased by 60 % and

t½ increased by approximately 30 % as compared to young healthy volunteers. However, there was no evidence of rabeprazole accumulation.

Following a 20 mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and t½ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolizers whilst C_{max} had increased by only 40 %.

Domperidone

Domperidone is rapidly absorbed after oral administration with peak plasma concentrations occurring at approximately 1 hr after dosing.. The Cmax and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

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 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

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.

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively, The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax of domperidone is 2.9- and 1.5- fold higher, respectively, than in healthy subjects.

The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on Cmax and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment.

In subjects with renal insufficiency (creatinine clearance<30 ml/min/1.73m2) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers.

Since very little unchanged drug (approximately 1%) is excreted via the kidneys, it is unlikely that

the dose of a single administration needs to be adjusted in patients with renal insufficiency.

However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on severity of the impairment, and the dose may need to be reduced.

No pharmacokinetic data are available in the Pharmacokinetic properties.

Non-Clinical Properties

Animal Toxicology or Pharmacology

Rabeprazole

Non-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.

Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but *in vivo* micronucleus and *in vivo* and *in vitro* DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

Domperidone

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 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). 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.

Description

RABICIP D Capsule contains Rabeprazole and Domperidone.

Rabeprazole

rabeprazole sodium, which is a proton pump inhibitor. It is a substituted benzimidazole known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*–benzimidazole sodium salt. It has a molecular formula of C18H20N3NaO3S and a molecular weight of 381.42. Rabeprazole sodium is a white to off-white, hygroscopic powder. It is freely soluble in methanol and methylene chloride. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media and is more stable under alkaline conditions.

Domperidone

A specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mechanisms

Pharmaceutical Particulars

Incompatibilities

NA

Shelf-Life

As on Pack

Packaging Information

Each Strip contains 15 Capsules

Storage and Handling Instructions

Store below 25°C.Protect from light and moisture

Patient Counselling Information

What Rabicip D are and what they are used for

Rabicip D is a medicine which contains Rabeprazole and Domperidone

Rabeprazole

Rabeprazole belong to a group of medicines called Proton Pump Inhibitors (PPIs). Rabeprazole act by reducing the amount of acid made by the stomach. Rabeprazole are used to treat:

• ulcer in the upper part of the intestine (duodenal ulcer)

• gastro-esophageal reflux disease (GERD) with or without ulcer.

GERD is commonly referred to as inflammation of the gullet caused by acid and associated with heartburn. Heartburn is a burning feeling rising from the stomach or lower chest up towards the neck. Rabeprazole may be used as a long term treatment of GERD (GORD maintenance). Rabeprazole may also be used for the symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GERD).

• Zollinger-Ellison Syndrome, which is a condition when the stomach makes extremely high amounts of acid.

Domperidone

Domperidone belongs to a group of medicines called 'dopamine antagonists'. This medicine is used to treat nausea (feeling sick) and vomiting (being sick) in adults and adolescents (12 years of age and older and weighing 35 kg or more).

Do not take if you have an allergy to the drug

Do not take this medicine if you

• are allergic to rabeprazole sodium, 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

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:

• atazanavir (used to treat HIV); it is not recommended to take Rabeprazole if you are taking atazanavir.

• ketoconazole or itraconazole (used to treat infections caused by a fungus).

Domperidone

Do not take Domperidone if you are taking medicine to treat:

• fungal infections such as azole antifungals, specifically oral ketoconazole, fluconazole or voriconazole

• bacterial infections, specifically erythromycin, clarithromycin, telithromycin, moxifloxacin, pentamidine (these are antibiotics)

• heart problems or high blood pressure (e.g., amiodarone, dronedarone, quinidine, disopyramide, dofetilide, sotalol, diltiazem, verapamil)

• psychoses (e.g., haloperidol, pimozide, sertindole)

• depression (e.g., citalopram, escitalopram)

• gastro-intestinal disorders (e.g., cisapride, dolasetron, prucalopride) • allergy (e.g., mequitazine, mizolastine)

• malaria (in particular halofantrine)

• AIDS/HIV (protease inhibitors)

• Hepatitis C (e.g., telaprevir) • cancer (e.g., toremifene, vandetanib, vincamine)

• certain other medicines (e.g., bepridil, diphemanil, methadone) 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.

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: Once capsule once daily

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?

Rabeprazole

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 Rabeprazole and contact a doctor immediately:

• sudden wheezing, swelling of your lips, face or body, rash, fainting or difficulties swallowing (severe allergic reaction).

• yellow skin, dark urine and tiredness which can be symptoms of liver problems.

• reddening of the skin with blisters or peeling and may be associated with a high fever and joint pains. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis.

Common side effects (may affect up to 1 in 10 people):

• cough, sore throat (inflammation of the pharynx), runny nose.

• nausea, vomiting, abdominal pain, diarrhoea, constipation, wind (flatulence).

• back pain, non-specific pain. • weakness or loss of strength, flu like symptoms.

• sleeplessness.

• headache, dizziness.

• infection.

• benign polyps in the stomach.

Uncommon side effects (may affect up to 1 in 100 people):

• nervousness.

• sleepiness. • inflammation of the bronchial tubes (bronchitis), inflammation of the sinuses (sinusitis).

• indigestion, dry mouth, belching.

• rash, skin redness (erythema).

• muscle pains, joint pains, leg cramps.

• urinary tract infection.

• chest pain, chills, fever.

• increased liver enzymes, which is measured by blood tests.

• fracture of the hip, wrist or spine.

Rare side effects (may affect up to 1 in 1,000 people):

• blood problems such as reduced number of white cells or platelets. This can cause weakness, bruising or make infections more likely.

• increased number of white blood cells.

• allergic reactions including facial swelling, low blood pressure and breathing difficulties.

• loss of appetite.

• depression.

• visual disturbance.

• inflammation of the stomach, inflammation of the mouth, taste disturbance.

• inflammation of the liver, jaundice (yellowing of the skin or eyes), brain disturbance associated with liver failure (hepatic encephalopathy).

• itching, sweating, skin blisters.

• kidney inflammation (interstitial nephritis).

• increased weight.

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

• sudden onset of severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains (erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis

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

• low levels of sodium in the blood.

• confusion.

• swelling of the feet and ankles.

• enlarged breasts in men.

• If you are on Rabeprazole for more than three months it is possible that the levels of magnesium in your blood may fall. Low levels of magnesium can be seen as fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate. If you get any of these symptoms, please tell your doctor promptly. Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. Your doctor may decide to perform regular blood tests to monitor your levels of magnesium.

• rash, possibly with pain in the joints.

• inflammation of the gut (leading to diarrhoea).

Domperidone

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

Other unwanted effects that have been observed with Domperidone are listed below:

Common (may affect up to 1 in 10 people):

• Dry mouth Uncommon (may affect up to 1 in 100 people):

• Anxiety

• Agitation

• Nervousness

• Loss of interest in sex or diminished interest in sex

• Headache

• Sleepiness

• Diarrhoea

• Rash

• Itchiness

• Hives

• Painful or tender breasts

• Milk discharge from breasts

• A general feeling of weakness

• Feeling dizzy

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

• Upward movement of the eyes • Stopped menstrual periods in women

• Enlarged breasts in men

• Inability to urinate

• Changes in certain laboratory test results

• Restless legs syndrome (uncomfortable feeling, with an irresistible urge to move your legs, and sometimes arms and other parts of your body)

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, hypersensitivity.

How should I store this medicine?

Keep this medicine out of the sight and reach of children.

Store below 25°C. Store in the original package in order to protect from moisture. 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 to

protect the environment.

General information about the safe and effective use of this medicine.

Rabeprazole

Do not take Rabeprazole if you

• are pregnant or breast-feeding.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Rabeprazole if you

• are allergic to other proton pump inhibitors.

• have or have had any liver problems.

• are taking a medicine called atazanavir (used to treat HIV).

• have reduced body stores or risk factors for reduced vitamin B12 and receive long term treatment with rabeprazole sodium. As with all acid reducing agents, rabeprazole sodium may lead to a reduced absorption of vitamin B12.

• if you are due to have a specific blood test (Chromogranin A).

• if you have ever had a skin reaction after treatment with a medicine similar to

Rabeprazole that reduces stomach acid. If you get a rash on your skin, especially in areas exposed to the sun, tell your doctor as soon as you can, as you may need to stop your treatment with Rabeprazole. Remember to also mention any other ill effects like pain in your joints.

If the above applies to you, consult your doctor before taking Rabeprazole. Your doctor may perform or have performed an additional investigation called an endoscopy in order to diagnose your condition and/or exclude malignant disease.

The possibility of stomach and oesophageal tumours should be excluded before the treatment is started. If you take Rabeprazole on a long-term basis (longer than one year) your doctor will probably monitor, you regularly. You should report any new or different symptoms whenever you see your doctor. Taking a proton pump inhibitor like Rabeprazole, especially over a period of more than one year, may slightly increase your risk of fracture of the hip, wrist or spine. Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can increase the risk of osteoporosis).

Talk to your doctor straight away if you experience severe (watery or bloody) or persistent diarrhoea with symptoms such as fever, abdominal pain or tenderness, as rabeprazole has been associated with a small increase in infectious diarrhoea

Some abnormal blood values have been reported during treatment with Rabeprazole. Usually, the values become normal when the treatment is discontinued. Children Rabeprazole are not recommended for use in children.

Pregnancy and breast-feeding

Rabeprazole must not be used during pregnancy and breast-feeding. If you are pregnant or breast-

feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist 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, occasionally rabeprazole can cause sleepiness. Therefore, driving and operating complex machinery should be avoided if you are affected

Domperidone

Do Not take Domperidone if:

• You have black, tarry bowel motions (stools) or notice blood in your bowel motions. This could be a sign of bleeding in the stomach or intestines

• You have a blockage or tear in your intestines

• You have a tumour of the pituitary gland called a prolactinoma.

• have a disorder known as phenylketonuria (a metabolic disorder)

• if you have a moderate or severe liver disease • if your ECG (electrocardiogram) shows a heart problem called "prolonged QT corrected interval"

• if you have or had a problem where your heart cannot pump the blood round your body as well as it should (condition called heart failure).

• if you have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood.

• if you are taking certain medicines

Do not take domperidone if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine. If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Domperidone. Do this even if they have applied in the past.

Warnings and precautions

Before taking this medicine contact your doctor if you:

• suffer from liver problems (liver function impairment or failure) (see “Do not take this medicinal product”)

• suffer from kidney problems (kidney function impairment or failure). It is advisable to ask your doctor for advice in case of prolonged treatment as you may need to take a lower dose or take this medicine less often, and your doctor may want to examine you regularly.

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 30mg per day. The risk also increases when domperidone is given together with some drugs. Tell your doctor or pharmacist if you are taking drugs to treat infection (fungal infections or bacterial infection) and/or if you have heart problems or AIDS/HIV (see section other medicines and Domperidone).

Domperidone should be used at the lowest effective dose. While taking domperidone, contact your doctor if you experience heart rhythm disorders such as palpitations, trouble breathing, loss of consciousness. Treatment with domperidone should be stopped. Adolescents weighing less than 35 kg and children Domperidone should not be given to adolescents 12 years of age and older weighing less than 35 kg, or in any children less than 12 years of age, as it is not effective in these age groups.

Taking Domperidone with food and drink

Domperidone should be taken before meals.

Pregnancy and breast-feeding

Talk to your doctor or pharmacist before taking Domperidone if:

• You are pregnant, might become pregnant or think you may be pregnant

• You are 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

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.

What are the ingredients in this medicine?

Each Hard Gelatin Capsule Contains

Rabeprazole Sodium IP …20mg

(As enteric coated pellets)

Domperidone IP……30mg

(As sustained release pellets)

Colours: Ferric Oxide (Red) USP.NF, Brilliant

Blue Lake and Titanium Dioxide I.P

Approved Colour used in capsule shell

Any other information

None.

Details of the Manufacturer

Mfd. By Cipla Ltd.

Registered Office:

Cipla House, Peninsula Business Park,

Ganpatrao Kadam Marg

Lower Parel

Mumbai – 400 013, India

Details of Permission or Licence Number with Date

M.L. No. MNB/15/880 dated 12/10/2015

Date of Revision

15/01/2020