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

VELOZ D

1. Generic Name

Rabeprazole sodium and Domperidone sustained release capsules 20 mg+30 mg

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Rabeprazole Sodium I.P……20 mg (as enteric coated pellets)

Domperidone Maleate I.P. equivalent to Domperidone……30 mg (in sustained release

form) Colour: Red Oxide of Iron

Approved colours used in hard gelatin capsules shell

The excipients used are Lactose monohydrate, ferric oxide red, hydroxy propyl methyl celu k4m, polyvinyl pyrrolidone (k30), crosspovidone xl-10, colloidal silicon dioxide, colloidal silicon dioxide, magnesium stearate, talc, magnesium oxide, sodium hydroxide.

3. Dosage form and strength

Dosage form: Capsule

Strength: Domperidone 30 mg; Rabeprazole 20 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of Gastroesophageal reflux not responding to Rabeprazole alone.

4.2 Posology and method of administration

One capsule once daily preferably before meal or as directed by physician.

4.3 Contraindications

Veloz D is contraindicated in the following situations:

- Known hypersensitivity to active substance or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma)
- when stimulation of the gastric motility could be harmful e.g in patients with gastro-intestinal haemorrhage, mechanical obstruction or perforation
- in patients with moderate or severe hepatic impairment
- in patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure
- co-administration with QT-prolonging drugs, at the exception of apomorphine
- co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)
- pregnancy and during breast feeding

4.4 Special warnings and precautions for use

Domperidone

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone.

These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

Reported 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 adolescents 12 years of age and older.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac

symptoms**.** Use with apomorphine

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

Renal impairment

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

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 (PPI) or substituted benzimidazoles cannot be excluded.

Patients should be cautioned that rabeprazole capsules should not be chewed or crushed, but should be swallowed whole.

Rabeprazole is not recommended for use in children, as there is no experience of its use in this group.

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

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

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

Co-administration of atazanavir with rabeprazole is not recommended.

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

PPIs, 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 older people or in presence of other recognised risk factors. Observational studies suggest that PPIs 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.

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.

Concomitant use of rabeprazole with methotrexate

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

Influence on vitamin B12 absorption

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

Subacute cutaneous lupus erythematosus (SCLE)

PPIs are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping rabeprazole. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, rabeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of PPI treatment.

Excipients

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

4.5 Drugs interactions

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 anti-psychotics (e.g., haloperidol, pimozide, sertindole)

· Certain anti-depressants (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).

· apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled. Please refer to the apomorphine SmPC.

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

· protease inhibitors

· systemic azole antifungals

· some macrolides (erythromycin, clarithromycin, 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 contra- indicated 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.

Rabeprazole

Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole.

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

Co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other PPIs. Therefore PPIs, including rabeprazole, should not be co- administered with atazanavir.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) 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.

4.6 Fertility, pregnancy and lactation

VELOZ D is contraindicated during pregnancy and breast feeding.

4.7 Effects on ability to drive and use machines

It is unlikely that VELOZ D 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.

4.8 Undesirable effects

Domperidone

Tabulated list of adverse reactions

The safety of domperidone was evaluated in clinical trials and in postmarketing experience. A reported clinical trial 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 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 terms and frequencies are applied:

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

System Organ Class	Adverse Drug Reaction Frequency		
	Common	**Uncommon**	**Not known**
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety	Agitation Nervousness
Nervous system disorders		Somnolence	Convulsion
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias
			Sudden cardiac death
			QTc prolongation
			Torsade de Pointes
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue		Rash Pruritus	Urticaria Angioedema
Renal and urinary			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.

Rabeprazole

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

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

Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (>1/10,000, <1/1000) 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	Infection				
Blood and the lymphatic system disorders			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system			Hypersensitivity[1,2]		
Metabolism and			Anorexia		Hyponatremia

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
nutrition disorders					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
Hepato-biliary Disorders			Hepatitis Jaundice Hepatic Encephalop		
Skin and		Rash	Pruritus	Erythema	Subacute cutaneous

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
subcutaneous tissue disorders		Erythema[2]	Sweating Bullous reactions[2]	multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	lupus erythematosus[4]
Musculoskeletal connective tissue and bone disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia, Fracture of the hip, wrist or spine[4]			
Renal and urinary Disorders		Urinary tract Infection	Interstitial nephritis		Acute kidney injury
Reproductive system and breast disorders					Gynaecomastia
General disorders and administration site conditions	Asthenia Influenza like Illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic Enzymes[3]	Weight increased		

[1]Includes facial swelling, hypotension and dyspnoea

[2]Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation

of therapy.

3Rare 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 VELOZ D is first initiated in such patients.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent **Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.**

4.9 Overdose

Domperidone

Symptoms

Symptoms of over dosage 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.**

Rabeprazole

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

5. Pharmacological properties

5.1 Mechanism of Action

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 oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

Rabeprazole

Mechanism of action

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump) The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the Veloz Dal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

5.2 Pharmacodynamic properties

Domperidone

Pharmacotherapeutic group: Propulsives

ATC code: A03FA03

Reported studies in man have shown oral domperidone to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

Rabeprazole

Pharmacotherapeutic group: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro- oesophageal reflux disease (GORD), PPIs,

ATC code: A02B C04

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 PPIs such as rabeprazole, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may possibly increase the risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

Serum gastrin effects

In reported 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.

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.

Reported 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.

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 PPIs 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.

5.3 Pharmacokinetic properties

Domperidone

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr 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 gastro-intestinal 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.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/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.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

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.

Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} 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 C_{max} 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.

Renal impairment

In subjects with severe renal insufficiency (creatinine clearance <30ml/min/1.73m^2) the elimination half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are 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 the severity of the impairment, and the dose may need to be reduced.

Paediatric population

No pharmacokinetic data are available in the paediatric population.

Rabeprazole

Absorption

VELOZ D is an enteric-coated (gastro-resistant) capusle formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile.

Absorption of rabeprazole therefore begins only after the capsule 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 $\pm$ 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.

Distribution

Rabeprazole is approximately 97% bound to human plasma

proteins. Metabolism and excretion

Rabeprazole sodium, as is the case with other members of the 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 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.

Gender

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

Renal dysfunction

In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤5ml/min/1.73m^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.

Hepatic dysfunction

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.

Older people

Elimination of rabeprazole was somewhat decreased in older people. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled, the C_{max} increased by 60% and t increased by approximately 30% as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.

CYP2C19 polymorphism

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

6. Nonclinical properties

Domperidone

Reported 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* pro-arrhythmic 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 45.4 ng/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 orally 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.

Rabeprazole

Reportedly, 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.

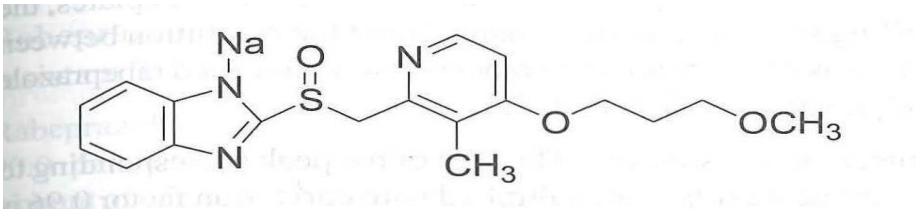
Reported studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but in vivo micronucleus and in vivo and in vitro DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

7. Description

Rabeprazole:

Rabeprazole sodium is 2-({[4-(3-methoxypropoxy)-3-methyl-

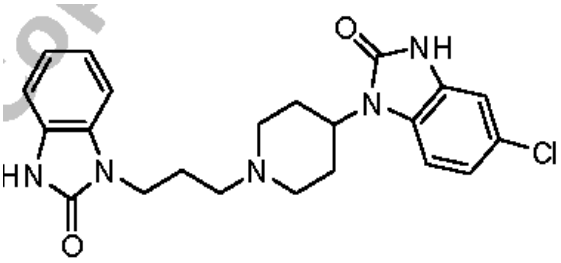
2-pyridinyl]methyl} sulphinyl)-lH-benzimidazole sodium having molecular formula of C18H20N3O3S,Na molecular weight is 381.4 the chemical structure is:



Rabeprazole is a white to light yellow, crystalline powder, hygroscopic. It is soluble in water.

Domperidone:

Domperidone IS 5-Chloro-1-[1-[3-(2-oxo-2,3-dihydro1H-benzimidazol-1-ylpropyl]piperidin-4-yl]- 1,3-dihydro-2H-benzimidazol-2 –one having molecular formula C22H24CLN5O2 Molecular weight is 425.9 the chemical structure is:



Domperidone is a white or almost white powder. Soluble in dimethylfonnamadie; slightly soluble in ethanol (95 per cent) and in methanol; practically insoluble in water.

Product Description:

VELOZ D

Green/White hard gelatin capsules printed with "Veloz D" and Torrent logo on the capsule shells, containing white to pale yellow pellets and one peach/brown red, capsule shaped, biconvex, uncoated bilayered tablets.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not available

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

VELOZ D is packed in strips of 10 Capsules.

8.4 Storage and handing instructions

Store below 25º C, protected from light and moisture. Keep all capsules away from children.

9. Patient counselling information

Package leaflet: information for the patient

VELOZ D

Read all of this 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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What VELOZ D is and what it is used for

The name of your medicine is VELOZ D sustained release capsules (called VELOZ D in this leaflet). VELOZ D contains a medicine called domperidone and rabeprazole. Domperidone belongs to a group of medicines called 'dopamine antagonists' and rabeprazole belongs to a group of medicines called 'Proton Pump Inhibitors' (PPIs).

VELOZ D is used for the treatment of Gastroesophageal reflux not responding to Rabeprazole alone.

9.2 What you need to know before you take VELOZ D

Do not take VELOZ D if:

- You are allergic (hypersensitive) to domperidone or any of the other ingredients of Veloz D Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You have a tumour of the pituitary gland (prolactinoma)
- You have a blockage or tear in your intestines
- 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 moderate or severe liver disease.
- Your ECG (electrocardiogram) shows a heart problem called "prolonged QT corrected interval".
- 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).
- You have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood.
- You are taking certain medicines (see "Other medicines and VELOZ D")
- You are pregnant or think that you are pregnant
- You are breast feeding

Do not take VELOZ D if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking VELOZ D.

Warnings and precautions

Before taking this medicine contact your doctor if:

- You suffer from liver problems (liver function impairment or failure)
- You 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.
- You are allergic to other proton pump inhibitor medicines or 'substituted benzimidazoles'.
- Blood and liver problems have been seen in some patients but often get better when VELOZ

D is stopped.
- You have a stomach tumour.
- You have ever had liver problems.
- If you are taking atazanavir- for HIV infection.
- If you 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 have ever had a skin reaction after treatment with a medicine similar to VELOZ D 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 VELOZ D. Remember to also mention any other ill-effects like pain in your joints.
- You are due to have a specific blood test (Chromogranin A).

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking VELOZ D.

VELOZ D 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. The risk also increases when VELOZ D 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 "Other medicines and VELOZ D).

VELOZ D should be used at the lowest effective dose in adults and adolescents 12 years of age and older and a body weight of 35kg or more.

While taking VELOZ D, contact your doctor if you experience heart rhythm disorders such as palpitations, trouble breathing, loss of consciousness. Treatment with VELOZ D should be stopped.

Other medicines and VELOZ D

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you can buy without a prescription, including herbal medicines. This is because VELOZ D can affect the way some other medicines work. Also, some medicines can affect the way VELOZ D works.

Do not take VELOZ D if you are taking medicine to treat:

- Fungal infections such as azole anti-fungals, 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)
- Cancer (e.g., toremifene, vandetanib, vincamine)
- Atazanavir– used to treat HIV-infection. VELOZ D may lower the amount of this type of medicine in your blood and they should not be used together.

- Methotrexate (a chemotherapy medicine used in high doses to treat cancer) – if you are taking a high dose of methotrexate, your doctor may temporarily stop your VELOZ D treatment.

Tell your doctor or pharmacist if you are taking drugs to treat infection, heart problems or AIDS/HIV.

VELOZ D and apomorphine

Before you use VELOZ D 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 the apomorphine leaflet.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before using VELOZ D.

Taking VELOZ D with food and drink

It is recommended to take VELOZ D before meals, as when taken after meals the absorption of the medicine is slightly delayed.

Pregnancy and breast-feeding

Do not use VELOZ D if you are pregnant or think you may be pregnant. Do not use VELOZ D if you are breast-feeding or planning to breast-feed.

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:

VELOZ D does not affect your ability to drive or use machines.

You may feel sleepy while taking VELOZ D. If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of VELOZ D

This medicine contains lactose. If you have been told that you cannot digest or tolerate some sugars, talk to your doctor before taking VELOZ D.

Children

VELOZ D should not be used in children.

If you experience severe (watery or bloody) diarrhoea with symptoms such as fever, abdominal pain or tenderness, stop taking VELOZ D and see a doctor straight away.

Taking a proton pump inhibitor like VELOZ D, especially over a period of more than one year, may slightly increase your risk of fracture in 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).

9.3 How to take VELOZ D

Taking this medicine

- Swallow the capsules whole with a drink of water.
- Take the capsules 15 to 30 minutes before a meal.
- Do not crush or chew them.
- Only remove capsule from the blister strip when it is time to take your medicine.
- Your doctor will tell you how many capsules to take and how long to take them for. This will depend on your condition.
- If you are taking this medicine for a long time, your doctor will want to monitor you.

If you take more VELOZ D than you should:

- If you have used or taken too many VELOZ D capsules contact your doctor, pharmacist or the poisons centre at your nearest hospital casualty department immediately, in particular if a child has taken too much. Take the carton and any capsules left with you. This is so the doctors know what you have taken. In the event of overdose, symptomatic treatment could be implemented. An ECG monitoring could be undertaken, because of the possibility of a heart problem called prolonged QT interval.
- The signs of taking more than you should include feeling sleepy, confused, uncontrolled movements (especially in children) which include unusual eye movements, unusual movements of the tongue or abnormal posture (such as a twisted neck).

If you forget to take VELOZ D:

- If you forget to take VELOZ D, take it as soon as you remember.
- However if it is almost time for the next dose, wait until that is due and then continue as normal.
- Do not take a double dose to make up for a forgotten dose.

9.4 Possible side effects

Like all medicines, VELOZ D can have side effects, although not everybody gets them.

Stop taking VELOZ D and see your doctor or go to a hospital straightaway if:

- You get swelling of the hands, feet, ankles, face, lips or throat which may cause difficulty in swallowing or breathing. You could also notice an itchy, lumpy rash (hives) or nettle rash (urticaria). This may mean you are having an allergic reaction to VELOZ D.
- You notice any uncontrolled movements. These include irregular eye movements, unusual movements of the tongue, and abnormal posture such as a twisted neck, trembling and muscle stiffness. This is more likely to happen in children. These symptoms should stop once you stop taking VELOZ D.
- You have a very fast or unusual heartbeat. This could be a sign of a life-threatening heart problem.
- You have a fit (seizure).
- Frequent infections, such as a sore throat or high temperature (fever), or ulcers in your mouth or throat
- Bruising or bleeding easily

Other side effects include:

Common (affects less than 1 in 10 people)

- Dry mouth
- Infections
- Difficulty sleeping
- Headache or feeling dizzy
- Cough, runny nose or sore throat (pharyngitis)
- Effects on your stomach or gut such as stomach pain, diarrhoea, wind (flatulence), feeling sick (nausea), being sick (vomiting) or constipation
- Aches or back pain
- Weakness or flu-like symptoms
- Benign polyps in the stomach

Uncommon (affects less than 1 in 100 people)

- Lowering of sexual drive (libido) in men

- Feeling anxious
- Feeling drowsy
- Headaches
- Diarrhoea
- Itchy skin
- Unusual production of breast milk in men and women
- Painful or tender breasts
- A general feeling of weakness
- Chest infection (bronchitis)
- Painful and blocked sinuses (sinusitis)
- Indigestion or belching
- Muscle, leg or joint pain
- Fractures of the hip, wrist and spine
- Bladder infection (urinary tract infection)
- Chest pain
- Chills or fever
- Changes in how your liver is working (shown in blood tests)

Not known (Frequency cannot be estimated from the available data)

- 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. Veloz D 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. Veloz D should be used at the lowest effective dose in adults and adolescents 12 years of age and older and a body weight of 35kg or more.
- Feeling agitated or irritable
- Feeling more nervous than usual
- Abnormal eye movements
- Inability to urinate
- Breast enlargement in men
- In women, menstrual periods may be irregular or stop

Rare (affect less than 1 in 1,000 people)

- Loss of appetite (Anorexia)
- Depression
- Hypersensitivity (includes allergic reactions)
- Visual disturbance
- Sore mouth (stomatitis) or taste disturbance
- Upset stomach or stomach pain
- Sweating
- Kidney problems
- Weight gain
- Changes in white blood cells (shown in blood tests) which may result in frequent infection
- Reduction in blood platelets resulting in bleeding or bruising more easily than normal

Other possible side effects (unknown frequency)

- Fluid retention
- Inflammation of the gut (leading to diarrhoea)

- Low blood levels of sodium which can cause tiredness and confusion, muscle twitching, fits and coma
- Patients who have previously had liver problems may very rarely get encephalopathy (a brain disease)"
- Kidney injury
- Rash, possibly with pain in the joints

If you are on VELOZ D 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.

Do not be concerned by this list of side effects. You may not get any of them.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5 How to store VELOZ D

Store below 25ºC, protected from light and moisture. Keep all capsules away from children.

9.6 Contents of the pack and other information

VELOZ D is packed in strips of 10 Capsules. VELOZ D contains rabeprazole and domperidone.

Green/White hard gelatin capsules printed with "Veloz D" and Torrent logo on the capsule shells, containing white to pale yellow pellets and one peach/brown red, capsule shaped, biconvex, uncoated bilayered tablets.

The excipients used are: lactose monohydrate, ferric oxide red, hydroxy propyl methyl celu k4m, polyvinyl pyrrolidone (k30), crosspovidone xl-10, colloidal silicon dioxide, colloidal silicon dioxide, magnesium stearate, talc, magnesium oxide, sodium hydroxide.

10. Details of manufacturer

Torrent Pharmaceuticals Ltd
Vill. Bhud & Makhnu Majra, Teh .Baddi-173
205, Dist. Solan (H.P.), INDIA.

11. Details of permission or licence number with date

MNB/05/183 issued on 22.09.2010

12. Date of revision

Feb-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
IN/VELOZ D 20mg, 30mg/Feb-22/06/PI