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

VELOZ M

1. Generic Name

Rabeprazole sodium and mosapride citrate sustained release capsules

2. Qualitative and quantitative composition

VELOZ M CAP

Each hard gelatin capsule contains:

Rabeprazole Sodium I.P. 20 mg

(as enteric coated pellets)

Mosapride citrate Dihydrate I.P equivalent to

Mosapride citrate Anhydrous 15 mg

(In sustained release form)

Colour: Red Oxide of Iron and Yellow Oxide of Iron

Approved colours used in hard gelatin capsules shell

The other excipients are as below:

The excipients used are talc, poly ethylene glycol, met.acid&eth.acr.co, lactose, magnesium stearate, polyvinyl pyrrolidone, colloidal silicon dioxide , colloidal silicon dioxide, hydroxy propyl methyl celu (hydroxy propyl methyl celu (metho k4m), iso propyl alcohol, hydroxy propyl methyl celu, ferric oxide yellow, ferric oxide red, microcrystalline cellu, croscarmellose sodium.

3. Dosage form and strength

Dosage Form: sustained release capsules

Strength: Rabeprazole Sodium - 20 & Mosapride citrate Anhydrous 15 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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

VELOZ M is contra-indicated in pregnancy and during breast feeding.

VELOZ M is contraindicated in the patients with GI hemorrhage, mechanical obstruction, or perforation.

4.4 Special warnings and precautions for use

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 VELOZ M.

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 VELOZ M should not be chewed or crushed, but should be swallowed whole.

VELOZ M 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 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 VELOZ M in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with VELOZ M is first initiated in such patients.

Co-administration of atazanavir with VELOZ M is not recommended.

Treatment with PPIs, including VELOZ M, 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 VELOZ M 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.

<u>Concomitant use of rabeprazole with methotrexate</u>

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.

<u>Influence on vitamin B12 absorption</u>

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 VELOZ M. 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, VELOZ M 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.

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Mosapride citrate(should not be used for more than 2 weeks in patients if no clinically therapeutic outcome is observed.

Important Precautions: When this drug is used for the treatment of gastrointestinal symptoms associated with chronic gastritis, after administration for a certain period of time (usually 2 weeks),the gastrointestinal symptoms should be assessed for improvement and the necessity of continuing administration should be evaluated.

This drug should not be administered for a long period of time, without adequate evaluation, because fulminant hepatitis, severe hepatic function disorder, and jaundice may occur. During administration of this drug, the patients should be carefully monitored and if any abnormality is observed, this drug should be discontinued immediately and appropriate measures taken. Furthermore, the patients should be instructed to discontinue the drug and contact a physician or other healthcare professional should they observe any symptoms such as malaise, anorexia, thick urine, and conjunctive bulbi coloring yellow after administration of this drug.

Use in the Elderly: Since in the elderly patients their physiological function in the kidneys and the liver are reduced in general, this drug should be administered with care by monitoring patients' condition. If any adverse reactions are found, appropriate measures such as reducing the dose (e.g. to 7.5 mg daily) should be given.

4.5 Drugs interactions

RABEPRAZOLE SODIUM

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 sodium.

In reported clinical trials, antacids were used concomitantly with the administration of Rabeprazole sodium 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.

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Erythromycin: When erythromycin at 1,200 mg/day was concomitantly administered with this drug at 15 mg/day, in comparison with a single administration of mosapride, maximum blood concentration of mosapride increased from 42.1 ng/mL to 65.7 ng/mL, the half life was prolonged from 1.6 hours to 2.4 hours and AUC_{0-4} increased from 62 ng•hr/mL to 114 ng•hr/mL. (Healthy adult.)

Anticholinergic agents: There is a possibility that the effect of this drug may be attenuated. Therefore, in case of the concomitant use of anticholinergic agents, precautions such as taking the drugs at intervals should be taken. As gastroprokinetic effect of this drug is exerted by activation of the cholinergic nerves, concomitant use of anticholinergic agents may decrease the effect of this drug.

4.6 Fertility, pregnancy and lactation

RABEPRAZOLE SODIUM

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. VELOZ M is contraindicated during pregnancy.

Breast feeding

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

MOSAPRIDE

Pregnancy

There are no data on the safety of VELOZ M 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. VELOZ M is contraindicated during pregnancy. Administration of this drug to nursing mothers should be avoided. If administration is essential, nursing mothers should discontinue breast feeding during the treatment. [Animal (rat) experiments have shown that this drug is excreted in breast milk.]

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that VELOZ M 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

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 infestations	Infection				
Blood and the lymphatic system disorders	Neutropenia Leucopenia Thrombocytopenia Leucocytosis		Eosinophilia		
Cardiovascular system			Palpitation		
Immune system disorders			Hypersensitivity		
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,	Cough	Bronchitis			

thoracic and mediastinal disorders	Pharyngitis Rhinitis	Sinusitis			
Gastrointestinal Disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic Gland Polyps (Benign	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance Abdominal pain		Microscopic colitis Feeling abnormal distension Numbness of mouth (including tongue and lip, etc.)
Hepato-biliary Disorders			Fulminant hepatitis[5] Jaundice Hepatic dysfunction Hepatic Encephalopathy, Elevations of AST (GOT), ALT (GPT), ALP, gamma-GTP and bilirubin		
Skin and subcutaneous tissue disorders		Rash Erythema	Pruritus Sweating Bullous reactions	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnso	Subacute cutaneous lupus erythematosus Urticaria

				n syndro me (SJS)	
Musculoskeletal connectiv e tissue and bone disorders	Non- specific pain Back pain	Myalgia Leg cramps Arthralgia			
Renal and urinary Disorders		Urinary tract Infection	Interstitial nephritis		Acute kidney injury
Reproductive system and breast disorders					Gynaecomas t ia
General disorders and administration site conditions	Asthenia Influenza like Illness	Chest pain Chills Pyrexia	Elevation of triglyceride		Malaise Tremor
Investigations		Increase d hepatic Enzymes	Weight increased		

1. Includes facial swelling, hypotension and dyspnoea
2. Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.
3. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with VELOZ M is first initiated in such patients.
4. See Special warnings and precautions for use
5. Since fulminant hepatitis, serious hepatic dysfunction accompanied with marked elevations of AST (GOT), ALT (GPT) and gamma-GTP, etc. and jaundice may occur and some of them were fatal, the patient should be monitored carefully and if any abnormalities are found, discontinue the administration immediately and give appropriate measures.

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In different clinical trials, adverse reactions were observed in 40 (4.0%) out of 998 patients. The main adverse reactions were diarrhea/loose stools (1.8%), dry mouth (0.5%), malaise (0.3%), etc. Abnormal laboratory values were observed in 30 (3.8%) of 792 cases and included increased

eosinophils (1.1%), triglycerides (1.0%), SGOT, SGPT, ALP and ?-GTP (0.4% each).

Commonly observed adverse events in Mosapride clinical trials are summarized below.

Body system	**Adverse effects**
Gastrointestinal	Diarrhea/ loose stools, dry mouth, abdominal pain
Hepatic	Increased SGOT, SGPT, ALP, ?-GTP
Cardiovascular	Palpitation
Others	Malaise, dizziness/ light-headed feeling, eosinophilia, increased

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor. 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

Experience to date with deliberate or accidental overdose is limited. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. VELOZ M 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

RABEPRAZOLE SODIUM

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 M cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

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In the gastric emptying test for healthy adults and patients with chronic gastritis, single administration of 5 mg of this drug enhanced gastric emptying.

Gastroprokinetic Effect: This drug increased gastric and duodenal motility after meals in conscious dogs.

Gastric Emptying Enhancing Effect: This drug enhances gastric emptying of liquid (in mice and rats) and solid (in rats) content. The gastric emptying enhancing effect was decreased after one week repeated administration (in rats).

5.2 Pharmacodynamic properties

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 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.

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 coadministered 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with VELOZ M in one or more subsets of the paediatric population in the treatment Gastro-Oesophageal Reflux Disease.

The European Medicines Agency has waived the obligation to submit the results of studies with VELOZ M in all subsets of the paediatric population in the treatment of Zollinger-Ellison syndrome, duodenal ulcer and gastric ulcer.

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Pharmacotherapeutic group: Alimentary tract and metabolism, drugs for functional gastrointestinal disorders

ATC code: A03FA09

Mechanism of Action:

This drug is a selective 5-HT4 receptor agonist. It is considered that this drug stimulates 5-HT4 receptors in the gastrointestinal nerve plexus, which increases the release of acetylcholine, resulting in enhancement of gastrointestinal motility and gastric emptying.

5.3 Pharmacokinetic properties

Absorption

Absorption of rabeprazole begins only after the it 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) 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.

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 ^{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.

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 $\leq$5ml/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.

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

$t_{½}$ 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 $t_{½}$ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst C_{max} had increased by only 40%.

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Plasma Concentration: (5 healthy adults under fasting conditions, single administration of 5 mg mosapride citrate)

Plasma Protein Binding Rate: 99.0% [in vitro, human serum, at a concentration of 1 μg/mL, methods of ultrafiltration or equilibrium dialysis].

Main Metabolites and Metabolic Pathway: Main metabolite: des-4-fluorobenzyl compound.

Metabolic pathway: Mosapride citrate is metabolized mainly in the liver, where the 4-fluorobenzyl group is removed, followed by oxidation of the morpholine ring at position 5, and hydroxylation of the benzene ring at position 3.

Excretion Route and Excretion Rate: Excretion route: In urine and feces.

Excretion rate: In urine collected for 48 hours after administration, 0.1% was excreted as unchanged compound and 7.0% was excreted as the main metabolite (des-4-fluorobenzyl compound). (Healthy adults, single administration of 5 mg of mosapride citrate under fasting conditions.)

Metabolic Enzyme: Cytochrome P-450 sub-family: mainly CYP3A4.

6. Nonclinical properties

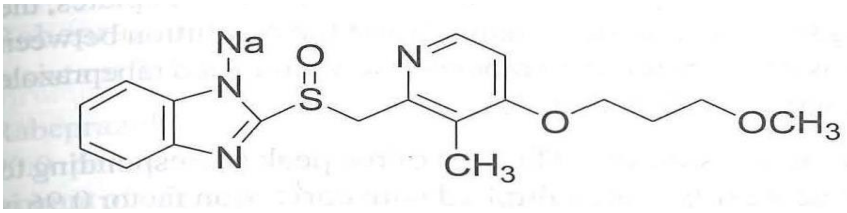
Non-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.

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.

7. Description

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:

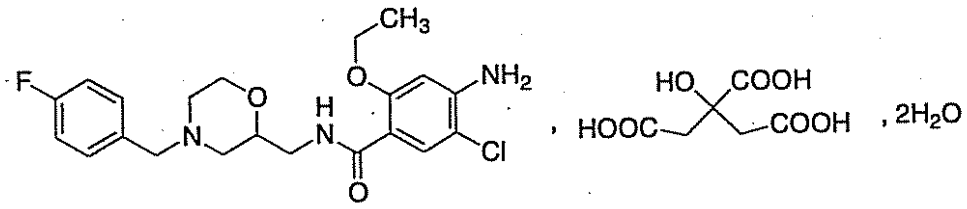


Rabeprazole is a white to light yellow, crystalline powder,

hygroscopic. It is soluble in water.

Mosapride Citrate Dihydrate:

MOsapride Citrate Dihydrate is (RS)-4-amino- 5-chloro 2-ethoxy N-{[4-(4-FLUOROBENZYL)-2-MORPHOLINYL]METHYL} benzamide citrate dehydrate. having molecular formula C21H25CLFN3O3,C6H8O7,2H2O Molecular weight is 650.0 the chemical structure is:



Mosapride Citrate Dihydrate A white or yellowish white crystalline powder. Soluble in dimethylfonnamide; sparingly soluble in methanol; practically insoluble in water.

Product Description:

VELOZ M

Purple/White hard gelatin capsules printed with "VELOZ M" and Torrent Logo (square emblem only) on the capsules shell, containind white to pale yellow pellets and one peach/white capsule shaped, biconvex, uncoated bilayered tablets.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

VELOZ M CAP is packed in strips of 10 Capsules.

8.4 Storage and handing instructions

Store below 25º C, protected from light and moisture.

9. Patient counselling information

Package leaflet: information for the patient

VELOZ M

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 M is and what it is used for

VELOZ M is hard gelatin capsule contains Rabeprazole sodium as enteric coated pellets and Mosapride citrate dihydrate in sustained release form. VELOZ M is used for the treatment of Gastroesophageal reflux not responding to Rabeprazole alone.

9.2 What you need to know before you take VELOZ M

Do not take VELOZ M if:

You are allergic (hypersensitive) to rabeprazole sodium, or any of the other ingredients of this medicine.

- You are pregnant or think that you are pregnant
- You are breast feeding

Do not use VELOZ M if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using VELOZ M

Warnings and precautions

Talk to your doctor or pharmacist before taking VELOZ M if:

- 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 M 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 M 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 M. 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 applies to you, talk to your doctor or pharmacist before using VELOZ M.

Children

VELOZ M should not be used in children.

Elderly

This drug should be administered to elderly patients with care and if any adverse reactions found then appropriate measures such as reducing the dose should be given.

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

Taking a proton pump inhibitor like VELOZ M, 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).

Other medicines and VELOZ M

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

- Ketoconazole or itraconazole – used to treat infections caused by a fungus. VELOZ M may lower the amount of this type of medicine in your blood. Your doctor may need to adjust your dose.
- Atazanavir– used to treat HIV-infection. VELOZ M 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 M treatment.
- Anticholinergic agents like atropine sulfate and butyl scopolamine bromide etc. which may decrease the effect of this drug.
- Erythromycin can increase the concentration of this drug in blood.

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

VELOZ M.

Pregnancy, breast feeding and fertility

- Do not use VELOZ M if you are pregnant or think you may be pregnant

- Do not use VELOZ M 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

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

9.3 How to take VELOZ M

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Taking this 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 are on long-term treatment you will need to see your doctor at regular intervals for review of your tablets and symptoms.

Patients with liver problems.

You should consult your doctor who will take special care when beginning treatment with VELOZ M and while you continue to be treated with VELOZ M.

If you take more VELOZ M than you should

If you take more VELOZ M than you should, talk to a doctor or go to a hospital straight away.

Take the medicine pack with you.

If you forget to take VELOZ M

- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual
- If you forget to take your medicine for more than 5 days, talk to your doctor before taking any more medicine
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose

If you stop taking VELOZ M

Relief of symptoms will normally occur before the ulcer has completely healed. It is important that you do not stop taking the tablets until told to do so by your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects are usually mild and improve without you having to stop taking this medicine.

Stop taking VELOZ M and see a doctor straight away if you notice any of the following side effects - you may need urgent medical treatment:

- Allergic reactions – the signs may include: sudden swelling of your face, difficulty breathing or low blood pressure which may cause fainting or collapse

- Frequent infections, such as a sore throat or high temperature (fever), or ulcers in your mouth or throat
- Bruising or bleeding easily

These side effects are rare (affect less than 1 in 1,000 people).

- Severe skin blistering, or soreness or ulcers in your mouth and throat
- These side effects are very rare (affect less than 1 in 10, 000 people).

Other possible side effects:

Common (affect less than 1 in 10 people)

- 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.
- Changes in blood count (eg. Neutropenia, Leucopenia, Thrombocytopenia, Leucocytosis)

Uncommon (affect less than 1 in 100 people)

- Feeling nervous or drowsy
- Chest infection (bronchitis)
- Painful and blocked sinuses (sinusitis)
- Dry mouth
- Indigestion or belching
- Skin rash or redness
- 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)

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
- Liver problems including yellowing of your skin and whites of your eyes (jaundice), elevation of liver function tests
- Itchy rash or blistering skin
- 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
- Rapid, strong, or irregular heartbeat
- Abdominal pain
- Elevation of triglyceride

Other possible side effects (unknown frequency)

- Breast swelling in men
- 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)
- Rash, possibly with pain in the joints
- Kidney injury
- Numbness of mouth
- Urticaria
- Tremor

If you are on VELOZ M 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. 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 M

Store below 25º C, protected from light and moisture.

9.6 Contents of the pack and other information

VELOZ M cap is packed in strips of 10 Capsules.

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 22.10.2010

12. Date of revision

Mar/2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/VELOZ M 20, 15mg/MAR-20/05/PI