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

VELOZ IT

1. **Generic Name**
   Rabeprazole Sodium (E.C.) 20 mg & Itopride Hydrochloride (S.R.) 150 mg Capsules
2. **Qualitative and quantitative composition**
   Each hard gelatin capsule contains:
   Rabeprazole Sodium I.P…..20 mg
   (as enteric coated pellets)
   Itopride Hydrochloride…..150 mg
   (as sustained release pellets)
   Excipients…….q.s.
   Colours: Ferric oxide USP-NF Red & Titanium Dioxide I.P.
   Approved colours used in capsule shell.
   The excipients used are ready to use pellets and Purified Talc.
3. **Dosage form and strength**
   Dosage Form: Hard Gelatin Capsules
   Strength: Rabeprazole Sodium – 20 & Itopride Hydrochloride - 150 mg
4. **Clinical particulars**

4.1 Therapeutic indication

The fixed dose combination of Rabeprazole with Itopride capsule is indicated for the treatment of gastroesophageal reflux disease (GERD) not responding adequately to Rabeprazole alone.

4.2 Posology and method of administration

Adults /older people

Active Duodenal Ulcer and Active Benign Gastric Ulcer: The recommended oral dose for both active duodenal ulcer and active benign gastric ulcer is 20 mg to be taken once daily in the morning.

Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing. Most patients with active benign gastric ulcer heal within six weeks. However again a few patients may require an additional six weeks of therapy to achieve healing.

Erosive or Ulcerative Gastro-Oesophageal Reflux Disease (GORD): The recommended oral dose for this condition is Veloz IT to be taken once daily for four to eight weeks.

Gastro-Oesophageal Reflux Disease Long-term Management (GORD Maintenance): For long-term management, a maintenance dose of Veloz IT once daily can be used depending upon patient response.

Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD): once daily in patients without oesophagitis. If symptom control has not been achieved during four weeks, the patient should be further investigated.

Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen taking once daily when needed.

Zollinger-Ellison Syndrome: The recommended adult starting dose is 60 mg once a day. The dose may be titrated upwards to 120 mg/day based on individual patient needs. Single daily doses up to 100 mg/day may be given. 120 mg dose may require divided doses, 60 mg twice daily. Treatment should continue for as long as clinically indicated.

For indications requiring once daily treatment Veloz IT capsules should be taken in the morning, before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.

Renal and hepatic impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment.

See section 4.4 in the treatment of patients with severe hepatic impairment**.**

Children

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

Method of administration

One capsule once daily or as directed by physician. It should be swallowed whole. It should be taken on an empty stomach (Take before meals).

4.3 Contraindications

Veloz IT is contraindicated in patients with known hypersensitivity to Rabeprazole, substituted benzimidazoles, Itopride or to any component of the formulation. Also contraindicated in patients in whom an increase in GI motility could be harmful eg, GI hemorrhage, mechanical obstruction or perforation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.

4.4 Special warnings and precautions for use

Rabeprazole

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with Rabeprazole.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

A risk of cross-hypersensitivity reactions with other proton pump inhibitor or substituted benzimidazoles cannot be excluded.

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 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 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 proton pump inhibitors, including Rabeprazole, may possibly increase the risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in older people or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors 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 proton pump inhibitor.
For patients expected to be on prolonged treatment or who take proton pump inhibitors with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting proton pump inhibitor 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)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Rabeprazole. SCLE after previous treatment with a proton pump

inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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 proton pump inhibitor treatment.

Itopride

Itopride is contraindicated in hypersensitivity to itopride or benzamides; lactation, GI hemorrhage, obstruction or perforation. Itopride may not be indicated for those suffering from Parkinson's disease or other conditions involving dopamine regulation issues. Itopride should be used with special caution in the young and the elderly. Little information is available at this time regarding the safe use of itopride during pregnancy. It may cause dizziness, do not drive a car or operate machinery while taking this medication.

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. Coadministration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with Rabeprazole.

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

Co-administration of atazanavir 300 mg/ritonavir 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 proton pump inhibitors. 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.

Itopride

Anticholinergic drugs may reduce the action of itopride. No interactions detected with warfarin, diazepam, diclofenac, nifedipine and nicardipine. Metabolic interactions are not to be expected because itopride is mainly metabolized by flavin monooxygenase.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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. Rabeprazole 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.

Itopride

Use in pregnancy

There are no adequate and well-controlled studies in pregnant women. Therefore, itopride HCl should not be used during pregnancy unless the benefits outweigh the potential risks.

Labor and Delivery

There are no known effects of itopride HCl on labor or delivery.

Use in lactation

Because itopride is excreted in milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Use in children

Safety of itopride in children< 16 years has not been established.

Use in the elderly

In general, appropriate caution should be exercised in the administration and monitoring of itopride HCl in elderly patients reflecting the greater frequency of decreased hepatic, renal function and of concomitant disease or other drug therapy. To be used with caution as it enhances the action of acetylcholine.

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that it 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 most commonly reported adverse drug reactions, during controlled clinical trials with Veloz IT were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-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 Leukopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity [1,2]		Anaphylactoid reaction
Metabolism and nutrition disorders			Anorexia		Hyponatremia Hypomagnesaemia[4]
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion Irritability
Nervous system disorders	Headache Dizziness	Somnolence			Tremor
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	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		Microscopic colitis Increased saliva

	Polyps (Benign)				
Hepato-biliary disorders			Hepatitis Jaundice Hepatic encephalopathy[3]		
Skin and subcutaneous tissue disorders		Rash Erythema[2]	Pruritus Sweating Bullous reactions[2]	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Subacute cutaneous lupus erythematosus[4] Itching Redness
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		
Reproductive system and breast disorders					Gynaecomastia Increased prolactin level
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia Fatigue			

Investigations		Increased hepatic enzymes[3]	Weight increased		

[1] Includes facial swelling, hypotension and dyspnoea

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

[3] Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Veloz IT is first initiated in such patients

[4] See Special warnings and precautions for use

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

Rabeprazole sodium

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

Itopride

There have been no reported cases of overdose in humans. In case of excessive overdose, the usual measures of gastric lavage and symptomatic therapy should be applied.

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

Itopride

Itopride activates the gastrointestinal propulsive motility by dopamine D2 receptors antagonistic action and acetylcholine esterase inhibitory action. Itopride activates acetylcholine release and inhibits its degradation.

In addition itopride has an antiemetic action which is based on interaction with dopamine D2 receptors in chemoreceptor zone. This action was demonstrated by dose dependent inhibition of apomorphine induced vomiting in dogs.

Itopride accelerates stomach emptying in humans.

In animal studies in dogs with a single dose administration itopride supported stomach emptying.

Itopride has high specific action in upper part of gastrointestinal tract.

Itopride does not influence plasma concentrations of gastrin.

5.2 Pharmacodynamic properties

Rabeprazole sodium

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

Anti-secretory Activity:

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

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

Serum Gastrin Effects:

In clinical studies patients were treated once daily with 10 or 20mg 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 20mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, oestrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone or somatotrophic hormone.

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

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

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

Itopride

Itopride hydrochloride's mechanism of action has been shown to involve an amplification of the prokinetic action of acetycholine in the gastrointestinal tract by increasing the release of acetycholine through the inhibition of the D2 receptors, as well as decreasing the metabolism of this transmitter by inhibiting the acetylcholinesterase enzyme.

5.3 Pharmacokinetic properties

Rabeprazole sodium

Absorption:

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

Absorption of rabeprazole therefore begins only after it leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20mg dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10mg to 40mg. Absolute bioavailability of an oral 20mg 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 proton pump inhibitor (PPI) class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although in vitro studies may not always be predictive of in vivo status these findings indicate that no interaction is expected between rabeprazole and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.

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

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 Cmax 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 Cmax 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 20mg of rabeprazole sodium, the AUC approximately doubled, the Cmax increased by 60% and t½ increased by approximately 30% as compared to young healthy volunteers. However, there was no evidence of rabeprazole accumulation.

CYP2C19 Polymorphism:

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

Itopride

Absorption

Itopride is absorbed rapidly and almost completely from gastrointestinal tract. Relative bioavailability about 60% is due to first-pass effect. Food does not affect bioavailability of the product. Maximum plasma concentrations are reached in 30 to 50 minutes after administration of 50 mg of itopride.

After repeated administration of doses in the range of 50 to 200 mg 3 times a day for period of 7 days, itopride and its metabolites have shown pharmacokinetics of linear type with minimal accumulation.

Distribution

About 96% of itopride is bound on plasma proteins, mainly albumin. Less than 15% of itopride bound part is bound on alpha-1-acid-glycoprotein.

In rats itopride is distributed extensively in the tissues (Vdß = 6.1 l/kg) except for central nervous system; high concentrations are reached in kidneys, small intestine, liver, adrenal glands and stomach. Protein binding in rats was lower than in humans (78% contrary to 96%). Penetration into the central nervous system was minimal. Itopride is excreted in milk of lactating rats.

Biotransformation

Itopride is extensively metabolised in liver in humans. Three metabolites were identified of which only one manifests minor activity without pharmacological significance (about 2 to 3% of itopride effect).

Itopride is metabolised by flavine monoxygenase (FMO3). The amount and efficacy of human FMO isoenzymes can be associated with genetic polymorphism which can result in rare autosomal recessive condition known as trimethylaminuria (fish odour syndrome). Biological half-life in patients with trimethylaminuria can be longer.

Pharmacokinetic *in vivo* studies of CYP-mediated reactions did not prove inhibition or induction CYP2C19 and CYP2E1 caused by itopride. Administration of itopride did not influence content of CYP or the activity of uridine-diphosphate-glucuronyl transferase.

Elimination

Itopride and its metabolites are primarily excreted by urine. The amount of excreted itopride and Noxide after oral single therapeutic dose to healthy volunteers was 3.7% and 75.4%, respectively.

Half-life of itopride is about 6 hours.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Rabeprazole sodium

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.

Itopride

Oral single lethal dose was 2,000 mg/kg in mice and rats and approximately 600 mg/kg in dogs.

Preclinical safety studies were carried out only with doses multiplicatively overrunning therapeutic human doses and found effect have only little importance for use of itopride in humans. In addition to it humans are less sensitive to hormonal effects observed in animals.

High doses of itopride (30 mg/kg/day) caused hyperprolactinaemia and secondary reversible hyperplasia of uterine mucosa in rats. Nevertheless this was not proved in dogs (dose up to 100 mg/kg/day) and monkeys (dose up to 300 mg/kg/day).

3-month toxicity study in dogs has revealed prostate atrophy after oral administration in dose 30 mg/kg/day. This effect was induced neither after 6-month administration of higher doses (100 mg/kg/day) in rats nor more higher doses (300 mg/kg/day) in monkeys.

Long-term studies of cancerogenity in animals have not been carried out.

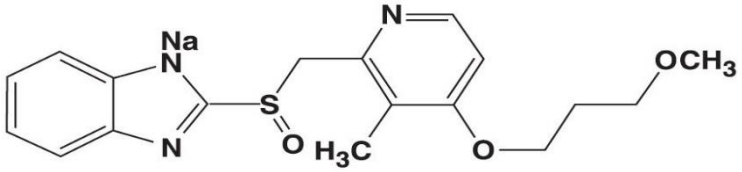
In series of *in vitro* and *in vivo* tests no clastogenic and mutagenic effects of itopride were found.

In fertility studies in female rats who were administered doses 30 mg/kg/day and higher hyperprolactinaemia and secondary prolongation of oestral cycle after were observed. Prolonged precoital interval was observed at doses 300 mg/kg/day. No side effect on copulation and fertility was proved.

7. Description

Rabeprazole Sodium

Rabeprazole Sodium is a substituted benzimidazole known chemically as 2-[[[4-(3--methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.42. The structural figure is:



Rabeprazole sodium is a white to slightly yellowish-white solid which is soluble in water.

Itopride Hydrochloride

Itopride Hydrochloride is chemically, N-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-3,4 dimethoxybenzamide;hydrochloride. It has an empirical formula of $C_{20}H_{27}ClN_2O_4$ and a molecular weight of 394.9.

Rabeprazole and Itopride Capsules are Red/Black '0' size hard gelatin capsules with Brown and white coloured spherical pellets. The excipients used are ready to use pellets and Purified Talc.

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 IT is available in strip pack of 10 capsules.

8.4 Storage and handing instructions

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

9. Patient Counselling Information

VELOZ IT

Rabeprazole Sodium (E.C.) 20 mg & Itopride Hydrochloride (S.R.) 150 mg Capsules

Read all of this leaflet carefully before you start using 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.

• 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. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.1 What Veloz IT is and what it is used for

The active ingredient in Veloz IT is Rabeprazole Sodium and Itopride Hydrochloride.

Rabeprazole Sodium: This belongs to a group of medicines called 'Proton Pump Inhibitors' (PPIs). They work by lowering the amount of acid that your stomach produces.

Itopride: This is a prokinetic benzamide derivative unlike domperidone. These inhibit dopamine and acetylcholine esterase enzyme and have a gastrokinetic effect.

The fixed dose combination of rabeprazole with Itopride capsule is indicated for the treatment of gastroesophageal reflux disease (GERD) not responding adequately to Rabeprazole alone.

9.2 What you need to know before you use Veloz IT

Do not take Veloz IT if:

- You are allergic (hypersensitive) to rabeprazole sodium, itopride 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 IT if any of the above applies to you. If you are not sure, talk to your doctor before using Veloz IT.

Warnings and precautions

Talk to your doctor before taking Veloz IT if:

- You are allergic to other proton pump inhibitor medicines or 'substituted benzimidazoles'.
- You are allergic to other prokinetic benzamide derivatives
- Blood and liver problems have been seen in some patients but often get better when Veloz IT 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 IT 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 IT. 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 before using Veloz IT.

Children

Veloz IT 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 IT and see a doctor straight away.

Taking a proton pump inhibitor like Veloz IT, 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 IT

Please tell your doctor 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 if you are taking any of the following medicines:

- Ketoconazole or itraconazole – used to treat infections caused by a fungus. Veloz IT 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 IT 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 IT treatment.

If you are not sure if any of the above apply to you, talk to your doctor before using Veloz IT.

Pregnancy, breast feeding and fertility

- Do not use Veloz IT if you are pregnant or think you may be pregnant
- Do not use Veloz IT 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 for advice before taking this medicine.

Driving and using machines

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

9.3 How to use Veloz IT

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

Taking this medicine

One capsule once daily or as directed by physician. It should be swallowed whole. It should be taken on an empty stomach (Take before meals).

Adults and older people

For 'gastro-oesophageal reflux disease' (GORD)

Treatment of moderate to severe symptoms (symptomatic GORD)

- The usual dose is one Veloz IT once a day for up to 4 weeks
- Take the capsule in the morning before eating
- If your condition returns after 4 weeks treatment, your doctor may tell you to take one Veloz IT as and when you require it.

Treatment of more severe symptoms (erosive or ulcerative GORD)

- The usual dose is one Veloz IT once a day for 4 to 8 weeks
- Take the capsule in the morning before eating

Long-term treatment of symptoms (GORD maintenance)

- The usual dose is one Veloz IT once a day for as long as your doctor has told you.
- Take the capsule in the morning before eating.
- Your doctor will want to see you at regular intervals to check your symptoms and

dosage.

For ulcers of the stomach (peptic ulcers)

- The usual dose is one Veloz IT once a day for 6 weeks.
- Take the capsule in the morning before eating.
- Your doctor may tell you to take Veloz IT for another 6 weeks if your condition does not improve.

For ulcers of the intestine (duodenal ulcers)

- The usual dose is one Veloz IT once a day for 4 weeks.
- Take the capsule in the morning before eating.
- Your doctor may tell you to take Veloz IT for another 4 weeks if your condition does not improve.

Zollinger-Ellison Syndrome where excess acid is produced in the stomach

- The usual dose is three Veloz IT once a day to start with.
- The dose may then be adjusted by your doctor depending on how you respond to the treatment.

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

Patients with liver problems. You should consult your doctor who will take special care when beginning treatment with Veloz IT and while you continue to be treated with Veloz IT.

If you take more Veloz IT than you should

If you take more Veloz IT 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 IT

- 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 IT

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

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

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 IT 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.

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)
- 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

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

If you are on Veloz IT 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 IT

• Keep out of the sight and reach of children.

• Do not use the capsules after the expiry date stated on the carton (EXP).

• Store below 25°C, protected from light and moisture.

• Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What Veloz IT contains:

• The active substance are Rabeprazole Sodium 20 mg and Itopride Hydrochloride 150 mg.

• The excipients are ready to use pellets and Purified Talc.

What are the contents of the pack

Veloz IT is available in strip pack of 10 capsules.

10. Details of manufacturer

Manufactured by:

Hetero Labs Ltd. (Unit I)
Kalyanpur (Village), Chakkan Road, Baddi (Tehsil), Solan (Distt.) HP – 173205.

11. Details of permission or licence number with date

Mfg Lic No. MNB/06/328 issued on 24.08.2019

12. Date of revision

Feb 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/VELOZ IT 20, 150mg/FEB-21/06/PI