To be sold by retail on the prescription of a Registered Medical Practitioner only

VONOTOR

1. **Generic Name**

   Vonoprazan Tablets 10 mg & 20 mg

2. **Qualitative and quantitative Composition:**

   VONOTOR 10

   Each film coated tablet contains:

   Vonoprazan Fumarate

   equivalent to Vonoprazan…….10 mg

   Excipients……q.s

   Colours: Titanium Dioxide I.P. and Yellow Oxide of Iron

   Excipients are Microcrystalline cellulose 102, Mannitol SD 200, Crosscarmellose sodium, Hydroxy propyl cellulose, Fumaric acid, Isopropyl alcohol, Purified water, Magnesium stearate, HPMC 2910/Hypromellose 6 cPs, Mannitol, Polyethylene Glycol 6000, Talc, Titanium Dioxide, Yellow Iron Oxide.

   VONOTOR 20

   Each film coated tablet contains:

   Vonoprazan Fumarate

   equivalent to Vonoprazan…….20 mg

   Excipients……q.s

   Colours: Titanium Dioxide I.P. and Red Oxide of Iron

   Excipients are Microcrystalline cellulose 102, Mannitol SD 200, Crosscarmellose sodium, Hydroxy propyl cellulose, Fumaric acid, Isopropyl alcohol, Purified water, Magnesium stearate, HPMC 2910/Hypromellose 6 cPs, Mannitol, Polyethylene Glycol 6000, Talc, Titanium Dioxide, Red Iron Oxide.

3. **Dosage form and strength**

   Dosage form: Film Coated Tablet

   Strength: Vonoprazan Tablets 10 mg / 20 mg

4. **Clinical particulars**

4.1. Therapeutic indication

- Treatment of reflux esophagitis (RE).
- Treatment of gastric ulcer (GU).
- Treatment of duodenal ulcer (DU).
- Prevention of recurrence of gastric ulcer or duodenal ulcer during low-dose aspirin administration.
- Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs administration.

- Adjunct to Helicobacter pylon eradication associated with: gastric ulcer, duodenal ulcer, gastric MALT lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage cancer, or helicobacter pylori gastritis.

4.2. Posology and method of administration

Posology

Reflux esophagitis (erosive esophagitis)

- The usual dose is 20 mg of vonoprazan once a day. Administration should be limited to 4 weeks. However, when the effect is insufficient, treatment may be continued for up to 8 weeks.

Gastric Ulcer

- The usual dose is 20 mg of vonoprazan once a day. Administration should be limited to 8 weeks.

Duodenal Ulcer

- The usual dose is 20 mg of vonoprazan once a day. Administration should be limited to 6 weeks.

Prevention of recurrence of gastric ulcer or duodenal ulcer during low-dose aspirin administration

- The usual dose is 10 mg of vonoprazan once a day.

Adjunct to Helicobacter pylori eradication

- Usually, the following 3 drugs are orally administered at the same time twice daily for 7 days: 20 mg vonoprazan, 750 mg amoxicillin hydrate, and 200 mg clarithromycin. The dose of clarithromycin may be appropriately increased as required; however, the upper limit is 400 mg twice daily or physician judgement.

  When Helicobacter pylori eradication treatment with 3 drugs consisting of a proton pump inhibitor, amoxicillin hydrate, and clarithromycin fails, alternative treatment with the following 3 drugs is recommended; 20 mg vonoprazan, 750 mg amoxicillin hydrate, and 250 m metronidazole, orally administered at the same time twice daily for 7 days. The doses of antibiotic should follow the respective label recommendations for H. pylori eradication.

Method of Administration

Vonoprazan can be taken without regard to food or timing of food.

Special Populations

***Elderly Patients*:**

Since the physiological functions such as hepatic or renal function are decreased in elderly patients in general, vonoprazan should be carefully administered.

***Paediatric Patients*:**

Vonoprazan has not been studied in patients under 18 years of age.

***Impaired Renal Function*:**

a. Healing of Erosive Esophagitis:

The recommended dosage of Vonoprazan in adult patients with renal impairment is described in Table below.

Recommended Vonoprazan Dosage in Healing of Erosive Esophagitis Patients with Renal Impairment:

Estimated Glomerular Filtration Rate (GFR)	Recommended Dosage
30 mL/minute or greater	20 mg once daily
Less than 30 mL/minute	10 mg once daily

Maintenance of Healed Erosive Esophagitis:

The recommended dosage of Vonoprazan in adult patients with renal impairment is the same as for adult patients with normal renal function.

b. Treatment of H. pylori Infection:

The recommended dosage of Vonoprazan in adult patients with renal impairment is described in Table below.

Recommended Vonoprazan Dosage in Treatment of H. pylori Infection Patients with Renal lmpairment[a]:

Estimated Glomerular Filtration Rate (GFR)	Recommended Dosage
30 mL/minute or greater	20 mg twice daily
Less than 30 mL/minute	Use is not recommended

[a] Also refer to the Dosage and Administration section of the amoxicillin and clarithromycin prescribing information for dosage recommendations in patients with renal impairment.

***Impaired Hepatic Function*:**

a. Healing of Erosive Esophagitis:

The recommended dosage of Vonoprazan in adult patients with hepatic impairment is described in Table below.

Recommended Vonoprazan Dosage in Healing of Erosive Esophagitis Patients with Hepatic Impairment:

Classification	Recommended Dosage
Child-Pugh Class A	20 mg once daily
Child-Pugh Class B	10 mg once daily
Child-Pugh Class C	10 mg once daily

Maintenance of Healed Erosive Esophagitis:

The recommended dosage of Vonoprazan in adult patients with hepatic impairment is the same as for patients with normal hepatic function.

b. Treatment of H. pylori Infection:

The recommended dosage of Vonoprazan in adult patients with hepatic impairment is described in Table below.

Recommended Vonoprazan Dosage in the Treatment of H. pylori Infection Patients with Hepatic Impairment:

Classification	Recommended Dosage
Child-Pugh Class A	20 mg twice daily
Child-Pugh Class B	Use is not recommended
Child-Pugh Class C	Use is not recommended

4.3. Contraindications

- Vonoprazan is contraindicated in patients with a known hypersensitivity to vonoprazan or any component of Vonoprazan. Reactions have included anaphylactic shock.

- Vonoprazan is contraindicated with rilpivirine-containing products.
- For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with Vonoprazan, refer to the Contraindications section of the corresponding prescribing information.

4.4. Special warnings and precautions for use

Presence of Gastric Malignancy

In adults, symptomatic response to therapy with Vonoprazan does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in patients who have a suboptimal response or an early symptomatic relapse after completing treatment with Vonoprazan. In older patients, also consider endoscopy.

Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been reported with Vonoprazan. If suspected, discontinue Vonoprazan and evaluate patients with suspected acute TIN.

Clostridioides difficile-Associated Diarrhea

Published observational studies suggest that proton pump inhibitors (PPIs) may be associated with an increased risk of Clostridioides difficile-associated diarrhea (CDAD), especially in hospitalized patients. Vonoprazan, another drug that blocks the proton pump to inhibit gastric acid production, may also increase the risk of CDAD. Consider CDAD in patients with diarrhea that does not improve. Use the shortest duration of Vonoprazan appropriate to the condition being treated.

CDAD has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with Vonoprazan, refer to Warnings and Precautions section of the corresponding prescribing information.

Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high dose, defined as multiple daily doses, and long-term therapy (a year or longer). Bone fracture, including osteoporosis-related fracture, has also been reported with vonoprazan. Use the shortest duration of Vonoprazan appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with Vonoprazan. Discontinue Vonoprazan at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Vitamin B12 (Cobalamin) Deficiency

Long-term use of acid-suppressing drugs can lead to malabsorption of Vitamin B12 caused by hypo- or achlorhydria. Vitamin B12 deficiency has been reported post marketing with vonoprazan. If clinical symptoms consistent with Vitamin B12 deficiency are observed in patients treated with Vonoprazan consider further workup.

Hypomagnesemia and Mineral Metabolism

Hypomagnesemia has been reported post marketing with vonoprazan. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients.

Consider monitoring magnesium levels prior to initiation of Vonoprazan and periodically in patients expected to be on prolonged treatment, in patients taking drugs that may have increased toxicity in the presence of hypomagnesemia (e.g., digoxin), or drugs that may cause hypomagnesemia (e.g., diuretics). Treatment of hypomagnesemia may require magnesium replacement and discontinuation of Vonoprazan.

Consider monitoring magnesium and calcium levels prior to initiation of Vonoprazan and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium, as necessary. If hypocalcemia is refractory to treatment, consider discontinuing Vonoprazan.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Temporarily discontinue Vonoprazan treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Fundic Gland Polyps

Use of Vonoprazan is associated with a risk of fundic gland polyps that increases with long-term use, especially beyond one year. Fundic gland polyps have been reported with vonoprazan in clinical trials and post-marketing use with PPIs. Most patients who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of Vonoprazan appropriate to the condition being treated.

4.5. Drug interactions.

Drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with Vonoprazan and instructions for preventing or managing them.

These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse reactions or loss of efficacy.

Consult the labeling of concomitantly used drugs to obtain further information about interactions with Vonoprazan.

Drug Interactions Affecting Drugs Co-Administered with Vonoprazan and Interactions with Diagnostics

Drugs Dependent on Gastric pH for Absorption		
Antiretrovirals		
Clinical Effect	Vonoprazan reduces intragastric acidity which may alter the absorption of antiretroviral drugs leading to changes in the safety and/or effectiveness.	
Prevention or Management	Rilpivirine-containing products	Concomitant use with Vonoprazan is contraindicated.

	Atazanavir Nelfinavir	Avoid concomitant use with Vonoprazan.
	Other antiretrovirals	See the prescribing information of other antiretroviral drugs dependent on gastric pH for absorption prior to concomitant use with Vonoprazan.
Other Drugs (e.g., iron salts, Erlotinib, Dasatinib, Nilotinib, Mycophenolate Mofetil, Ketoconazole/Itraconazole)		
Clinical Effect	Vonoprazan reduces intragastric acidity, which may decrease the absorption of drugs reducing their effectiveness.	
Prevention or Management	See the prescribing information for other drugs dependent on gastric pH for absorption	
Combination Therapy with Clarithromycin and/or Amoxicillin		
Clinical Effect	Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and are contraindicated. Amoxicillin also has drug interactions.	
Prevention or Management	See Contraindications and Warnings and Precautions in the prescribing information for clarithromycin. See Drug Interactions in the prescribing information for amoxicillin.	
Certain CYP3A Substrates where minimal concentration changes may lead to serious toxicities		
Clinical Effect	Vonoprazan is a weak CYP3A inhibitor. Vonoprazan may increase exposure of CYP3A4 substrates, which may increase the risk of adverse reactions related to these substrates.	
Prevention or Management	Frequent monitoring for concentrations and/or adverse reactions related to the substrate drugs when used with Vonoprazan. Dosage reduction of substrate drugs may be needed. See prescribing information for the relevant substrate drugs.	
CYP2C19 Substrates (e.g., Clopidogrel, Citalopram, Cilostazol)		
Clinical Effect	Vonoprazan is a CYP2C19 inhibitor. Vonoprazan may reduce plasma concentrations of the active metabolite of clopidogrel and may cause reduction in platelet inhibition. Vonoprazan may increase exposure of CYP2C19 substrate drugs (e.g., citalopram, cilostazol).	
Prevention or Management	Clopidogrel	Carefully monitor the efficacy of clopidogrel and consider alternative anti-platelet therapy.
	Citalopram and Cilostazol	Carefully monitor patients for adverse reactions associated with citalopram and cilostazol. See the prescribing information for dosage adjustments.
Chromogranin (CgA) Test for Neuroendocrine Tumors		
Clinical Effect	Vonoprazan reduces intragastric acidity, which increases CgA levels and may cause false positive results in diagnostic investigations for neuroendocrine tumors.	
Prevention or Management	Assess CgA levels at least 14 days after stopping Vonoprazan treatment and repeat the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), use the same commercial laboratory for testing, as reference ranges between tests may vary.	
Interaction with Secretin Stimulation Test		
Clinical Effect	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.	

Prevention or Management	Temporarily stop Vonoprazan at least 14 days before assessing to allow gastrin levels to return to baseline.

Drug Interactions Affecting Vonoprazan When Co-Administered with Other Drugs

Strong or Moderate CYP3A4 Inducers	
Clinical Effect	Vonoprazan is a CYP3A substrate. Strong or moderate CYP3A inducers decrease vonoprazan exposure, which may reduce the effectiveness of Vonoprazan.
Prevention or Management	Avoid concomitant use with Vonoprazan.

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

Pregnancy

No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are pregnant. In a rat toxicology study, embryo-foetal toxicity was observed following exposure of more than approximately 28 times of the exposure (AUC) at the maximum clinical dose (40 mg/day) of vonoprazan. As a precaution, vonoprazan should not be administered to women who are or may be pregnant, unless the expected therapeutic benefit is thought to outweigh any possible risk.

Lactation

No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are lactating. It is unknown whether vonoprazan is excreted in human milk. In animal studies it has been shown that vonoprazan was excreted in milk. During treatment with vonoprazan, nursing should be avoided if the administration of this drug is necessary for the mother.

Pediatric use

The safety and effectiveness of vonoprazan is not established in pediatric patients.

Geriatric use

No overall differences in safety or effectiveness were observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between the geriatric and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

No clinically meaningful differences in the pharmacokinetics of vonoprazan are predicted in patients 65 years of age and older compared to younger adult patients.

Renal Impairment

Healing of Erosive Esophagitis: No dosage adjustment of vonoprazan is recommended in patients with mild to moderate renal impairment (eGFR 30 to 89 mL/min). Dosage reduction is recommended in patients with severe renal impairment (eGFR < 30 mL/min).

Maintenance of Healed Erosive Esophagitis: No dosage adjustment of vonoprazan is recommended in patients with any degree of renal impairment.

Treatment of H. pylori Infection: Use of vonoprazan is not recommended for the treatment of *H. pylori* infection in patients with severe renal impairment (eGFR < 30mL/min).

Hepatic Impairment

Healing of Erosive Esophagitis: No dosage adjustment of vonoprazan is recommended in patients with mild hepatic impairment (Child- Pugh A). Dosage reduction is recommended in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C).

Maintenance of Healed Erosive Esophagitis: No dosage adjustment of vonoprazan for the maintenance of healed erosive esophagitis is recommended in patients with any degree of hepatic impairment.

Treatment of H. pylori Infection: Use of vonoprazan is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C).

4.7. Effects on ability to drive and use machines.

The influence of vonoprazan on the ability to drive or use machines is unknown.

4.8. Undesirable effects

The following serious adverse reactions are described:

- Acute Tubulointerstitial Nephritis
- Clostridioides difficile-Associated Diarrhoea
- Bone Fracture
- Severe Cutaneous Adverse Reactions
- Vitamin B12 (Cobalamin) Deficiency
- Hypomagnesemia and Mineral Metabolism
- Fundic Gland Polyps

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Healing of Erosive Esophagitis and Maintenance of Healed Erosive Esophagitis

The safety of Vonoprazan was evaluated in a randomized, active-controlled, double-blind two-phase trial for the healing of erosive esophagitis (2 to 8 weeks) and maintenance of healed erosive esophagitis (through 24 weeks) conducted in the United States and Europe.

Adverse reactions reported in at least 2% of patients in the Vonoprazan arm in the healing phase are presented in below table.

Adverse Reactions[a] in a Clinical Trial of Adult Patients with All Grades of Erosive Esophagitis[b] (2 to 8 Week Healing Phase)

Adverse Reactions	Vonoprazan 20 mg Once Daily N=514 (%)	Lansoprazole 30 mg Once Daily N=510 (%)
Gastritis[c]	3	2
Diarrhea[c]	2	3
Abdominal distension	2	1
Abdominal pain[c]	2	1
Nausea	2	1

[a] Reported in at least 2% of patients in the Vonoprazan arm.

[b] The trial was not designed to support comparative claims for Vonoprazan for the adverse reactions reported in this table.

[c] Represents a grouped term and includes related terms.

Adverse reactions reported in at least 3% of patients in the vonoprazan arm of the maintenance phase are shown in below table.

Adverse Reactions[a] in a Clinical Trial of Adult Patients with All Grades of Erosive Esophagitis[b] (24 Week Maintenance Phase)

Adverse Reactions	Vonoprazan 10mgOnceDaily N=296 (%)	Lansoprazole 15 mg Once Daily N=297 (%)
Gastritis[c]	6	3
Abdominal pain[c]	4	2
Dyspepsia	4	3
Hypertension[c]	3	2
Urinary tract infection	3	2

[a] Reported in at least 3% of patients in the Vonoprazan arm.

[b] The trial was not designed to support comparative claims for Vonoprazan for the adverse reactions reported in this table.

[c] Represents grouped term and includes related terms.

Other Clinical Trials of Erosive Esophagitis:

Adverse reactions reported in the United States trial were similar to those reported in 4 additional randomized, active-controlled, double-blind studies of vonoprazan compared to lansoprazole conducted outside of the United States (two eight-week trials of healing of erosive esophagitis and 24-week maintenance of healed erosive esophagitis trials).

Less Common Adverse Reactions:

Adverse reactions reported in 1% or less of vonoprazan-treated patients in the healing or maintenance phase of the United States trial are:

Blood and lymphatic system disorders: anemia, lymphocytosis Cardiac disorders: tachycardia

Ear and labyrinth disorders: vertigo

Gastrointestinal disorders: duodenal polyp, dry mouth, dysphagia, eructation, flatulence, gastric polyps, vomiting

General disorders and administrative site conditions: asthenia, peripheral edema

Infections and infestations: upper respiratory infection

Investigations: increased liver function test

Metabolism and nutritional disorders: diabetes mellitus

Musculoskeletal system: bone fracture

Nervous system disorders: dizziness, headache, syncope

Psychiatric disorders: depression, insomnia

Renal and urinary disorders: tubulointerstitial nephritis

Skin and subcutaneous tissue disorders: eczema, rash, urticarial

Treatment of H. pylori Infection

The safety of vonoprazan, amoxicillin and clarithromycin was evaluated in 675 adult patients (aged 20 to 82 years) in clinical trials in the United States, Europe and Japan and vonoprazan and amoxicillin was evaluated in 348 adult patients (aged 20 to 80 years) in a clinical trial in the United States and Europe. All of the patients were screened and found to be positive for *H. pylori* infection.

The safety of vonoprazan, amoxicillin and clarithromycin (triple therapy) and vonoprazan and amoxicillin (dual therapy) was evaluated in a randomized, controlled, double-blind (triple therapy)/open-label (dual therapy) study conducted in the United States and Europe in treatment-naive *H. pylori*-positive adult patients.

Adverse Reactions Leading to Discontinuation:

Treatment discontinuation due to an adverse reaction occurred in 2.3% (8/346) of the patients treated with vonoprazan, amoxicillin and clarithromycin, 0.9% (3/348) of the patients treated with vonoprazan and amoxicillin, and 1.2% (4/345) of the patients treated with lansoprazole, amoxicillin and clarithromycin. The most common adverse reactions leading to discontinuation of vonoprazan, amoxicillin and clarithromycin were diarrhea (0.6%) and hypertension (0.6%) and the most common adverse reaction leading to discontinuation of vonoprazan and amoxicillin was rash (0.6%).

Most Common Adverse Reactions:

Adverse reactions reported in at least 2% of patients in any treatment arm are described in below table.

Adverse Reactions[a] in Adult Patients with *H. pylori* infection[b]

Adverse Reactions	Vonoprazan, Amoxicillin N=348 (%)	Vonoprazan, Amoxicillin, & Clarithromycin N=346 (%)	Lansoprazole, Amoxicillin, & Clarithromycin N=345 (%)
Diarrhea	5	4	10
Dysgeusia[c]	1	5	6
Vulvovaginal candidiasis[c]	2	3	1
Abdominal pain[c]	3	2	3
Headache	1	3	1
Hypertension[c]	1	2	1
Nasopharyngitis	2	<1	1

[a] Reported in at least 2% of patients in any treatment arm.

[b] These trials were not designed to support comparative claims for Vonoprazan-containing treatment arms for the adverse reactions reported in this table.

[c] Represents grouped term and includes related terms.

Less Common Adverse Reactions:

Adverse reactions reported in 2% or less of Vonoprazan-treated patients in the healing or maintenance phase of the United States trial are:

Blood and lymphatic system disorders: anemia, lymphocytosis, leukocytosis, leukopenia, neutropenia

Cardiac disorders: tachycardia, QT prolongation

Ear and labyrinth disorders: orbital edema

Gastrointestinal disorders: abdominal distension, constipation, dry mouth, duodenal polyp, duodenal ulcer, dyspepsia, flatulence, gastric ulcer, gastroesophageal reflux disease, hematochezia, large intestine polyp, rectal polyp, nausea, stomatitis, tongue discomfort, vomiting

Immune system disorders: drug hypersensitivity

Infections and infestations: anal fungal infection, gastrointestinal viral infection, oral fungal infection, pneumonia, tongue fungal infection, upper respiratory tract infection, urinary tract infection, viral infection

Investigations: increased liver function test

Metabolism and nutrition disorders: decreased appetite

Musculoskeletal system: bone fracture

Nervous system disorders: dizziness, syncope, ageusia, tension, headache

Psychiatric disorders: depression, insomnia, anxiety

Renal and urinary disorders: tubulointerstitial nephritis, renal hypertrophy, acute kidney injury

Reproductive system and breast disorders: vaginal discharge

Respiratory, thoracic and mediastinal disorders: cough, nasal polyps, oropharyngeal pain

Skin and subcutaneous tissue disorders: eczema, rash, urticaria, dermatitis, dry skin, rash

Post marketing Experience.

The following additional adverse reactions have been identified during post-approval use of vonoprazan outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: anaphylactic shock

Infections and infestations: *C. difficile* (with concomitant antibacterials).

Investigation: hypomagnesemia, hypokalemia, hypocalcemia, vitamin B12 deficiency

Hepatobiliary disorders: hepatic injury, hepatic failure, jaundice

Skin and subcutaneous tissue disorders: drug eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Reporting of 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: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

There is no experience of overdose with vonoprazan. Vonoprazan is not removed from the circulation by hemodialysis. If overdose occurs, treatment should be symptomatic and supportive.

Drug Abuse and Dependence

Vonoprazan has no known potential for abuse or dependence.

5. Pharmacological properties

5.1. Mechanism of action

Vonoprazan is a potassium competitive acid blocker (PCAB). Vonoprazan suppresses both basal and stimulated gastric acid secretion at the secretory surface of the gastric parietal cell through inhibition of the H+, K+-ATPase enzyme system in a potassium- competitive manner. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, vonoprazan has been characterized as a type of gastric proton-pump inhibitor, in that it blocks the final step of acid production. Vonoprazan does not require activation by acid. It may selectively concentrate in the parietal cells in both the resting and stimulated states. Vonoprazan binds to the active pumps in a noncovalent and reversible manner.

5.2. Pharmacodynamic activity

Antisecretory Activity

Following a single 10 mg or 20 mg dose of vonoprazan, the onset of the antisecretory effect as measured by intragastric pH occurs within 2 to 3 hours. The elevated intragastric pH levels compared to placebo increase with dose and are maintained for over 24 hours after dosing. The inhibitory effect of vonoprazan on acid secretion increases with repeated daily dosing and steady state is achieved by Day 4. The antisecretory effect of vonoprazan decreases following drug discontinuation although intragastric pH remained elevated compared to placebo for 24 to 48 hours following the dose on Day 7.

The effects of vonoprazan 10 mg or 20 mg once daily for 7 days on 24-hour intragastric pH in healthy subjects are shown in below table.

Effect of Vonoprazan 10 mg or 20 mg Once Daily on 24-Hour lntragastric pH at Baseline and on Days 1 and 7 in Healthy Subjects

Parameter	Vonoprazan 10 mg Once Daily (N=9)			Vonoprazan 20 mg Once Daily (N=9)		
	Base line	Day 1	Day 7	Base line	Day 1	Day 7
Mean lntragastric pH)	2.0	3.7	4.6	1.9	4.5	5.9
%Time lntragastric pH>4 (hours)	6.8 (2 h)	43.1 (10 h)	60.2 (14 h)	7.4 (2 h)	62.7 (15 h)	85.2 (20 h)
%Time lntragastric pH>6 (hours)	1.3 (<1 h)	20.7 (5 h)	34.3 (8 h)	0.9 (< 1 h)	29.0 (7 h)	57.8 (14 h)

Cardiac Electrophysiology

At a single dose of 120 mg (6-times the maximum recommended dose), vonoprazan does not prolong the QT interval to any clinically relevant extent.

Serum Gastrin Effects

The effect of vonoprazan on serum gastrin concentrations was evaluated in 514 patients for up to 8 weeks (healing phase) and in 592 patients for up to 6 months (maintenance phase). During the healing phase, the mean fasting gastrin levels at Week 2 increased from baseline after treatment with vonoprazan 20 mg and levels were similar at Week 2 and Week 8. In the 6-month maintenance phase, the mean gastrin levels remained elevated with vonoprazan 10 mg and 20 mg and the mean serum gastrin levels returned to normal within 4 weeks of discontinuation of treatment.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum CgA levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors.

Enterochromaffin-Like Cell (ECL) Effects

Human gastric biopsy specimens were obtained from 135 patients treated with vonoprazan 10 mg or 20 mg once daily for up to 260 weeks. An increase in the incidence of hyperplasia of the parietal cells and G-cells was observed, which is consistent with the pharmacological action of a potassium competitive acid blocker. No neoplastic changes were observed.

5.3 Pharmacokinetic properties

Steady state pharmacokinetic (PK) parameters for vonoprazan 10 mg or 20 mg following once daily administration and vonoprazan 20 mg following twice daily administration from data collected across multiple studies are summarized in below table.

Mean (%CV) Steady State Pharmacokinetic Parameters For Vonoprazan Following Once or Twice Daily Dosing

PK Parameter	Vonoprazan 10 mg	Vonoprazan 20 mg	
	Once Daily (N=30)	Once Daily (N=68)	Twice Daily (N=32)
T_{max} (h) median (min, max)	1.5 (0.75, 3.0)	2.0 (0.75, 5.0)	3.0 (1.0-6.0)
C_{max} (ng/mL)	11.7 (27.5)	26.1 (35.2)	37.8 (36.1)
AUC (h*ng/mL)	92.9 (33.1)[a]	230.9 (41.3)[a]	272.5 (30.5)[b]
t1/2Z (h)	7.7 (27.1)	7.9 (22.6)	6.8 (22.7)
CL/F (L/h)	120.2 (35.2)	100.2 (38.3)	81.3 (35.7)
V_Z/F (L)	1270.7 (26.6)	1114.0 (39.6)	782.7 (34.4)

[a] $AUC_{0\text{-}24h}$

[b] $AUC_{0\text{-}12h}$

C_{max} = Maximum plasma concentration, $AUC_{0\text{-}24h}$ = Area under the plasma concentration-time curve from time 0 to end of the 24-hour dosing interval, $AUC_{0\text{-}12h}$ = Area under the plasma concentration-time curve from time 0 to end of the 12-hour dosing interval, T_{max} = Time to reach C_{max}, $t_{1/2}$ = Elimination half-life, CL/F = Apparent oral clearance, V_Z/F = Apparent oral volume of distribution.

Absorption

Vonoprazan exhibits time independent pharmacokinetics and steady state concentrations are achieved by Day 3 to 4. After multiple doses of vonoprazan ranging from 10 to 40 mg (twice the maximum recommended dose) once daily for 7 days in healthy subjects, C_{max} and area under the plasma concentration time curve (AUC) values for vonoprazan increased in an approximately dose proportional manner.

There is little accumulation in plasma after once daily multiple doses, with an accumulation index ratio of less than 1.2 based on AUC for doses ranging from 10 to 40 mg (twice the maximum recommended dose).

Steady state plasma exposure of vonoprazan following 20 mg twice daily dosing ($AUC_{0\cdot12h}$ = 273 hr*ng/mL, N=10) was approximately 1.8-fold higher compared to the mean estimate from the same subjects on Day 1 ($AUC_{0\text{-}12h}$ =155 hr*ng/mL, N=10).

Effect of Food

In a food effect study in healthy subjects (N=24) who received vonoprazan 20 mg, a high-fat meal resulted in a 5% increase in C_{max}, a 15% increase in AUC, and a delay in median T_{max}, of 2 hours. These changes are not considered to be clinically significant.

Distribution

Plasma protein binding of vonoprazan ranged from 85 to 88% in healthy subjects and was independent of concentration from 0.1 to 10 mcg/mL.

Metabolism

Vonoprazan is metabolized to inactive metabolites via multiple pathways by a combination of cytochrome P450 (CYP) isoforms (CYP3A4/5, CYP2B6, CYP2C19, CYP2C9 and CYP2D6) along with sulfo- and glucuronosyl-transferases. CYP2C19 polymorphisms have been evaluated in clinical studies and there were no considerable differences in the pharmacokinetics of vonoprazan based on CYP2C19 metabolizer status

Excretion

Following oral administration of radiolabeled vonoprazan, approximately 67% of the radio labeled dose (8% as unchanged vonoprazan) was recovered in urine and 31% (1.4% as unchanged vonoprazan) was recovered in feces.

Special Populations

Impaired Renal Function

The effect of renal disorders on pharmacokinetics of vonoprazan was evaluated in subjects with normal renal function and patients with mild, moderate or severe renal disorder and patients with end-stage renal disease (ESRD). When administered a single dose of vonoprazan 20 mg the AUC_{∞} was higher by 1.3 to 2.4 times and the C_{max} higher by 1.2 to 1.8 times in patients with mild, moderate or severe renal disorder compared to subjects with normal renal function, indicating an increase in vonoprazan exposure with a reduction in renal function. The AUC∞ was higher by 1.3 times and the C_{max} higher by 1.2 times in ESRD patients compared to those in subjects with normal renal function.

Impaired Hepatic Function

The effect of hepatic disorders on pharmacokinetics of vonoprazan was evaluated in subjects with normal hepatic function and patients with mild, moderate or severe hepatic disorder. When administered a single dose of vonoprazan 20 mg, the AUC∞ was higher by1.2 to 2.6 times and the C_{max} were higher by 1.2 to 1.8 times in patients with mild, moderate or severe hepatic disorder, compared to subjects with normal hepatic function.

Age, Gender, Race

Vonoprazan has not been studied in patients under 18 years of age. There are no clinically relevant gender effects of vonoprazan. No dedicated ethnic comparison studies have been conducted with vonoprazan. The ethnic sensitivity analysis based on the International Conference for Harmonization (ICH) E5 principles was conducted to assess whether the molecular properties of vonoprazan were sensitive to ethnic factor differences, and whether the diagnosis, medical practice, treatment options, and other epidemiological factors for acid-related disorders would vary dramatically in areas other than Japan. It was concluded that vonoprazan is insensitive to ethnic factor differences.

Drug Interactions

Vonoprazan and Clarithromycin:

Healthy adult male subjects were administered with a single dose of vonoprazan (40 mg), 30 minutes after breakfast on day 1 and day 8, and with repeated dose of clarithromycin 500 mg (potency) 2 times daily 30 minutes before breakfast and dinner on day 3 – 9. The AUC_{∞} and C_{max} of vonoprazan increased by 1.6 times and 1.4 times, respectively, when concomitantly administered with clarithromycin compared to those of vonoprazan when administered alone.

Vonoprazan, Amoxicillin Hydrate and Clarithromycin:

The drug interaction study in healthy adult male subjects administered twice daily with vonoprazan 20 mg, amoxicillin hydrate 750 mg (potency) and clarithromycin 400 mg (potency) concomitantly for 7 days shows no effect on pharmacokinetics of unchanged amoxicillin, however, AUC12 and C_{max} of vonoprazan increased by 1.8 times and 1.9 times,

respectively, and AUC_{12} and C_{max} of unchanged clarithromycin increased by 1.5 times and 1.6 times, respectively.

Vonoprazan, Amoxicillin Hydrate and Metronidazole:

The drug interaction study in healthy adult male subjects administered twice daily with vonoprazan 20 mg, amoxicillin hydrate 750 mg (potency) and metronidazole 250 mg concomitantly for 7 days showed little difference in the pharmacokinetics of vonoprazan, when administered alone or as triple therapy. No difference was observed in the pharmacokinetics of metronidazole or amoxicillin when administered alone or as triple therapy.

Vonoprazan, Bismuth, Clarithromycin and Amoxicillin:

The drug interaction study in *Helicobacter pylori* positive adult subjects administered twice-daily vonoprazan 20 mg or lansoprazole 30 mg with tripotassium bismuth dicitrate 600 mg, clarithromycin 500 mg, and amoxicillin 1000 mg concomitantly for 14 days shows the lack of a clinically meaningful effect of vonoprazan on the pharmacokinetics of bismuth compared with lansoprazole.

Vonoprazan and low-dose Aspirin or Vonoprazan and NSAIDs:

The drug interaction study in healthy adult male subjects administered with vonoprazan 40 mg and aspirin 100 mg or NSAID (loxoprofen sodium 60 mg, diclofenac sodium 25 mg or meloxicam 10 mg) concomitantly showed no clear effect of low-dose aspirin or NSAIDs on pharmacokinetics of vonoprazan and of vonoprazan on pharmacokinetics of low-dose aspirin or NSAIDs.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis

Vonoprazan was non-carcinogenic in a long-term carcinogenicity study in mice when administered the drug daily via oral gavage for up to 2 years at 0.6, 20, 60, and 200 mg/kg/day. Treatment-related tumors, related to exaggerated pharmacology or sepsis-specificity, were noted in the stomach and liver. In the stomach, benign and malignant neuroendocrine cell tumors were observed at ≥20 (males) and ≥60 (females) mg/kg/day and ≥6 (males) and ≥60 (females) mg/kg/day, respectively. In the liver, increased incidences of hepatocellular adenoma and carcinoma were observed at ≥20 (males) and ≥60 (females) mg/kg/day, and at ≥60 (males) and 200 (females) mg/kg/day, respectively. Hyperplasia of the neuroendocrine cells and associated tumors in the stomach may be due to hypergastrinemia as a consequence of inhibiting gastric acid secretion. The hepatocellular tumors are likely rodent-specific findings that are attributed to prolonged induction of hepatic drug-metabolizing enzymes. The NOAEL was < 6 mg/kg/day.

Vonoprazan was non-carcinogenic in a long-term carcinogenicity study in rats administered the drug via oral gavage at 5, 15, 50, and 150 mg/kg/day. Treatment-related tumors, related to exaggerated pharmacology or species-specificity, were noted in the stomach and liver. In the stomach, benign and malignant neuroendocrine cell tumors were observed at ≥5 mg/kg/day except for malignant neuroendocrine tumor at 50 mg/kg/day (males). In some instances in benign and malignant neuroendocrine cell tumors, tumor cells showed eosinophilic change but these tumors were also judged to be of neuroendocrine cell origin. In the liver, increased incidences of hepatocellular adenoma and carcinoma were observed at ≥50 mg/kg/day except for hepatocellular carcinoma at 50 mg/kg/day (females). Tumor findings in the stomach and liver are believed to be due to hypergastrinemia as a consequence of inhibiting gastric acid secretion and rodent-specific induction of hepatic drug metabolizing enzymes, respectively.

The occurrence of 4 hepatocholangiocellular tumors at ≥50 mg/kg/day (males) were considered to be treatment-related because they were considered to be associated with induction of hepatocellular tumor, but pairwise comparison did not demonstrate a statistically significant effect.

Mutagenicity

Vonoprazan did not exhibit any mutagenic or clastogenic activity in the *in vitro* Ames assay, *in vitro* mammalian chromosome aberration assay, and *in vivo* rat micronucleus assay.

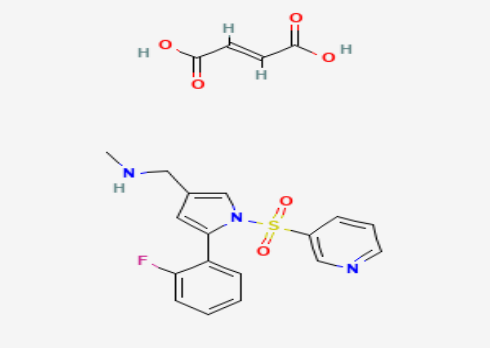
Impairment of Fertility

When administered daily via oral gavage to male and females rats there were no effects on sperm analysis, estrous cycles or number of corpora lutea observed at doses up to 300 mg/kg/dose. Males were administered vonoprazan prior to and during mating and females dosed for 2 weeks pre-mating through Gestation Day (GD) 6. The NOAEL for male and female general toxicity was 30 mg/kg/day and ≥ 300 mg/kg/day for reproductive function and early embryonic development.

7. Description

Vonoprazan Fumarate:

Vonoprazan Fumarate is (E)-but-2-enedioic acid;1-[5-(2-fluorophenyl)-1-pyridin-3-ylsulfonylpyrrol-3-yl]-N-methylmethanamine. The empirical formula is $C_{21}H_{20}FN_3O_6S$ and its molecular weight is 461.5 g/mol. The chemical structural formula is:



Vonoprazan Fumarate is white to off white crystalline powder.
It is Soluble in dimethyl sulphoxide, very slightly soluble in methanol and water.

VONOTOR 10

Vonoprazan Tablets 10 mg is Light yellow to yellow colored, biconvex, round shaped, film coated tablets, plain on both sides.

Excipients are Microcrystalline cellulose 102, Mannitol SD 200, Crosscarmellose sodium, Hydroxy propyl cellulose, Fumaric acid, Isopropyl alcohol, Purified water, Magnesium stearate, HPMC 2910/Hypromellose 6 cPs, Mannitol, Polyethylene Glycol 6000, Talc, Titanium Dioxide, Yellow Iron Oxide.

VONOTOR 20

Vonoprazan Tablets 20 mg is Light pink to pink colored, biconvex, oval shaped, film coated tablets breakline on both sides.

Excipients are Microcrystalline cellulose 102, Mannitol SD 200, Crosscarmellose sodium, Hydroxy propyl cellulose, Fumaric acid, Isopropyl alcohol, Purified water, Magnesium stearate, HPMC 2910/Hypromellose 6 cPs, Mannitol, Polyethylene Glycol 6000, Talc, Titanium Dioxide, Red Iron Oxide.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

VONOTOR 10 & 20 is available in pack of 10 Tablets.

8.4. Storage and handing instructions.

Store at a temperature not exceeding 30^0C, protected from light and moisture.

Keep out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

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 license number with date

Mfg. License No.: MNB/05/183

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD

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Ahmedabad-380 009, INDIA

IN/VONOTOR 10 mg & 20 mg/APR 2025/01/PI