To be sold by retail on the prescription of Gastroenterologist only

PRESCRIBING INFORMATION

Vonoprazan Tablets 10 mg & 20 mg

MSN VPR™

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1. Generic Name
Vonoprazan Tablets 10 mg
Vonoprazan Tablets 20 mg

2. Qualitative and quantitative composition
Vonoprazan Tablets 10 mg:
Each film coated tablet contains:
Vonoprazan fumarate equivalent to
Vonoprazan ..... 10 mg
Excipient ..... q.s.
Color: Ferric Oxide Red USP-NF & Titanium Dioxide IP

Vonoprazan Tablets 20 mg:
Each film coated tablet contains:
Vonoprazan fumarate equivalent to
Vonoprazan free base ..... 20 mg
Excipients..... q.s.
Color: Ferric Oxide Red USP-NF & Titanium Dioxide IP

3. Dosage form and strength
Dosage form: Immediate Release Tablets
Strength: 10 mg and 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 pylori (H. pylori)* 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

- *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.
- *Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs 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 mg 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 Patient 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.
- ***Pediatric Patients***
  Vonoprazan has not been studied in patients under 18 years of age.
- ***Impaired Renal Function***
  Healing of Erosive Esophagitis
  The recommended dosage of Vonoprazan in adult patients with renal impairment is described in Table 1 below:
  Table 1: 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 or Relief of Heartburn Associated with Non-Erosive Gastroesophageal Reflux Disease
  The recommended dosage of Vonoprazan in adult patients with renal impairment is the same as for adult patients with normal renal function.
  Treatment of H. pylori infection
  The recommended dosage of Vonoprazan in adult patients with renal impairment is described in Table 2 below:
  Table 2: Recommended Vonoprazan Dosage in Treatment of H. pylori Infection Patients with Renal Impairment:

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

- ***Impaired Hepatic Function***
  Healing of Erosive Esophagitis:
  The recommended dosage of Vonoprazan in adult patients with renal impairment is described in Table 3 below:

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 or Relief of Heartburn Associated with Non-Erosive Gastroesophageal Reflux Disease
  The recommended dosage of Vonoprazan in adult patients with hepatic impairment is the same as for adult patients with normal hepatic function.
  Treatment of H. pylori infection
  The recommended dosage of Vonoprazan in adult patients with hepatic impairment is described in Table 4 below:
  Table 4: Recommended Vonoprazan Dosage in 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
Hypersensitivity to the active ingredients or to any of the excipients.

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 diarrhoea 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 the 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 postmarketing 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 postmarketing 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 4 weeks 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 postmarketing 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
Table 5 and Table 6 include 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.

Table 5: 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	Avoid concomitant use with Vonoprazan.
	Nelfinavir	
	Rilpivirine-containing products	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 is contraindicated. Amoxicillin also has drug interactions.	
Prevention or Management	See Contraindications and Warnings and Precautions in the prescribing information for clarithromycin. See Drug I nteractions 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	Frequently monitor 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 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 4 weeks 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 4 weeks before assessing to allow gastrin levels to return to normal.	

Table 6: 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 and Lactation

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 (40mg/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 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.

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

Clinical Trials
Clinical trial data for expected adverse events is based on pooled safety analysis from the following studies: EE healing (CCT-001 and CCT-002), EE maintenance therapy (CCT-003 and OCT-001), GU healing (CCT-101), DU healing (CCT-102), prevention of recurrence of peptic ulcer associated with NSAID use (CCT-301, OCT-301 and OCT-303), prevention of recurrence of peptic ulcer associated with

300 mm

Front side 220 mm

BDR	**Aw Name :** MSN VPR 10/20 (Vonoprazan Tablets 10/20 mg)_Insert		**Client :** MSN Laboratories
	Artwork Code : YCGVTAXIN/I2	**Dosage :** Tablets	**Mfg. Site :** Halol Baska
	Size : 220 x 300 mm	**Folds :** 3(H) + 2(V)	**Folded Size :** 37.5 x 55.0 mm
	Paper : 41 GSM Bible Paper		
Generic Name Font & Size : NA		**Brand Name Font & Size :** NA	
Colors : CMYK Color ■ Black			
Instruction : Pantone Color Process			
Artwork History : XXXXXXXXXXXXXXX			

LDA use (CCT-302, OCT-302 and OCT-304) and treatment of non-erosive reflux disease (NERD; CCT-201). Although the study in patients with NERD has the placebo arm and is considered as the best data, the number of patients (N=449 and 278 for TAK-438 and placebo, respectively) is relatively small compared to the number of patients of all other active-comparator studies combined (N=3162 and 1392) for TAK-438 and AG-1749 [Lansoprazole], respectively). Therefore, the pooled safety data of active-comparator studies are used for the primary analysis. The safety data of CCT-201 study are analysed separately. (Note: AG-1749 (Lansoprazole) is the only comparator used in the comparator studies.) The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1. adverse reaction with Vonoprazan in clinical studies

Frequency/ System Organ Class*	Very Common	Common	Uncommon	Rare	Vary Rare	Not Know
Gastrointestinal Disorder		Diarrhoea Constipation	Nausea Abdominal distension			
Investigation			Gamma-Glutamyl transferase increased aspartame Aminotransferase increased Liver function test abnormal Alanine aminotransferase			

* ADRs included as preferred terms are are based on MedDRA version 21.0.

Post-marketing:
Following is a list of ADRs which have been observed in post-marketing (Frequency unknown):

Table 2. Adverse reactions with Vonoprazan in post-marketing setting System Organ Class

System Organ Class	Preferred Term
Immune system disorders	Drug hypersensitivity (including anaphylactic shock) Drug eruption Urticaria
Hepatobiliary disorders	Hepatotoxicity Jaundice
Skin and Subcutaneous tissue disorders	Rash Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis

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 Pharmacodynamic Properties

Mechanism of Action
Vonoprazan is a potassium competitive acid blocker (PCAB) and inhibits H+, K+-ATPase in a reversible and potassium-competitive manner. It does not require activation by acid. Vonoprazan is a strong base with a high affinity for the acid pump of gastric cells inhibiting gastric acid production.

5.2 Pharmacokinetic Properties groups
Following 7 day repeat once daily doses of Vonoprazan at doses of 10-40 mg, in healthy adult male subjects, $AUC_{t,ss}$ and C_{max} increase in a slightly greater than dose proportional manner. Steady state has been reached by day 3 of administration, since the trough level of the blood concentration of Vonoprazan is constant between day 3 and day 7 of administration.

In addition, Vonoprazan does not exhibit time-dependent pharmacokinetics.

The following table shows pharmacokinetic parameters of Vonoprazan on day 7 of administration.

Dose	10 mg	20 mg
$t_{max,ss}$ (h)	1.5 (0.75, 3.0)	1.5 (0.75, 3.0)
$C_{max,ss}$ (ng/mL)	12.0±1.8	23.3±6.6
$t_{1/2Z}$ (h)	7.0±1.6	6.1±1.2
$AUC_{T,SS}$ (h ng/mL)	79.5±16.1	151.6±40.3

Mean ± S.D. of 9 subjects ($t_{max,ss}$ is expressed by the median (minimum value, maximum value)

Absorption
Absolute bioavailability has not been determined. The pharmacokinetic parameters of Vonoprazan following single administration of Vonoprazan to healthy adult male subjects at 20 mg under fasting and fed conditions are presented in the table below

Dose Condition	**Under fasting**	**After meal**
$t_{max,ss}$ (h)	1.5 (1.0, 3.0)	3.0 (1.0, 4.0)
$C_{max,ss}$ (ng/mL)	24.3±6.6	26.8±9.6
$t_{1/2Z}$ (h)	7.7±1.0	7.7±1.2
AUC_{48}(h ng/mL)	222.1±69.7	238.3±71.1

Mean±S.D. of 12 subjects ($t_{max,ss}$ is expressed by the median (minimum value, maximum value)

Distribution
The mean binding rate is 85.2 to 88.0% when [14C] Vonoprazan in the range of 0.1 to 10 µg/mL is added to human plasma (*in vitro*).

Metabolism
Vonoprazan is metabolized mainly by hepatic drug-metabolizing enzyme CYP3A4 and partially by CYP2B6, CYP2C19 and CYP2D6. Vonoprazan is also metabolized by sulfotransferase SULT2A1 (*in vitro*).

Vonoprazan exhibits time-dependent inhibitory effect on CYP2B6, CYP2C19 and CYP3A4/5 (*in vitro*). In addition, Vonoprazan shows a slight concentration-dependent inductive effect on CYP1A2, but it shows little inductive effect on CYP2B6 and CYP3A4/5 (*in vitro*).

Excretion and Elimination
When radioactive-labeled drug (15 mg as Vonoprazan) is orally administered to healthy adult male subjects, 98.5% of the radioactivity administered is excreted into urine and feces by 168 hours after administration: 67.4% into urine and 31.1% into feces.

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 insentitive 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 Cmax 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 20mg, amoxicillin hydrate 750 mg (potency) and clarithromycin 400 mg (potency) concomitantly for 7 days shows no effect on pharmacokinetics of unchanged amoxicillin, however, AUC_{12} 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 20mg, 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. Preclinical Safety data

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.

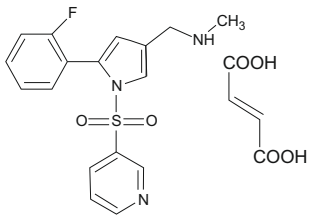
Vonoprazan was non-carcinogenic in a long term carcinogenicity study in rats administered the drug via oral gavage at 5, 15, 50, and 150 mg/kg/day. Treatment-related tumors, related to exaggerated pharmacology or species-specificity, were noted in the stomach and liver. In the stomach, benign and malignant 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.

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 is the active ingredient of Vonoprazan. The chemical name is 1-[5-(2-Fluorophenyl)-1-(Pyridin-3- yl-sulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine Monofumarate.

The Molecular weight is 461.46 and Molecular formula is C21H20FN3O6S. The structural formula is



8. Pharmaceutical particulars

8.1 Incompatibilities: There is no Incompatibilities

8.2 Shelf-life: 24 months

8.3 Packaging information: 10 Tablets in Alu-Alu Strip. Such 10 strips are packed in a mono-carton with a pack insert.

8.4 Storage and handing instructions: Store below 30°C

9. Patient Counselling Information

- Do not take Vonoprazan if you are allergic to vonoprazan or any of the other ingredients of this medicine.
- If you are currently taking a medicine containing the active substance atazanavir or rilpivirine, don't use Vonoprazan.
- Before you take Vonoprazan, tell your doctor if you:
  - o Have liver problems
  - o Have kidney problems
  - o Are pregnant or plan to become pregnant
  - o Are breastfeeding or plan to breastfeed. It is not known if Vonoprazan passes into breast milk. Do not breastfeed during treatment with Vonoprazan.
- Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
- Especially tell your doctor if you are taking any medication containing following active substance as: Clarithromycin (used to treat infection) or Atazanavir or Rilpivirine (used to treat HIV). Vonoprazan may affect or be affected by these drugs.

10. Details of manufacturer
BDR Pharmaceuticals Int'l Pvt. Ltd.,
Survey No. - 51/1/1, 51/1/2, 51/2, 52/1, 52/2/1, 52/2/2, 52/2/2 (p), 52/4, 52/5, 53/1, 53/2, 53/3, 54/1, 54/2, At - Vanseti Village, Po - Tajpura, Taluka - Halol, Dist. Panchmahal - 389 350.

11. Details of permission or licence number with date
Mfg. License No. G/25/2534 issued on 03/01/2022

12. Date of revision
September-2024

TM - Trademark Under Registration

MFLL0047-00
YCGVTAXIN/I2

300 mm

Front side 220 mm