SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Vonoprazan Tablets 20 mg (VONOGLAX 20)

2. Qualitative and quantitative composition
Each film coated tablet contains
Vonoprazan Fumarate
Eq. to Vonoprazan 20 mg
Excipients Q.S.
Colours: Ferric Oxide Red & Titanium Dioxide BP
Excipient(s) with known effect
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet
Brick red colour, round, biconvex, plain on both sides, film coated tablet.

4. Clinical particulars
4.1 Therapeutic indications
• for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
• to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults.
• in combination with amoxicillin for the treatment of *H. pylori* infection in adults.

4.2 Posology and method of administration
Posology
Healing of Erosive Esophagitis and Relief of Heartburn
- The recommended adult oral dosage is VONOPRAZAN 20 mg once daily for 8 weeks.

Maintenance of Healed Erosive Esophagitis and Relief of Heartburn
- The recommended adult oral dosage is VONOPRAZAN 10 mg once daily for up to 6 months.

Treatment of H. Pylori Infection
• Triple Therapy: The recommended adult oral dosage is VONOPRAZAN 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily (in the morning and evening, 12 hours apart) for 14 days.
• Dual Therapy: The recommended adult oral dose is VONOPRAZAN 20 mg given twice daily (in the morning and evening) plus amoxicillin 1,000 mg three times daily (in the morning, mid-day, and evening) for 14 days.
• Also refer to the amoxicillin and clarithromycin full prescribing information.

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

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.

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 Patients with Renal Impairment: Treatment of *H. pylori* Infection[a] Estimated GFR

Estimated 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.

Recommended Dosage in Patients with Hepatic Impairment

Healing of Erosive Esophagitis

The recommended dosage of VONOPRAZAN in adult patients with hepatic impairment is described in Table 3 below.

Table 3: Recommended VONOPRAZAN Dosage in Patients with Hepatic Impairment: Healing of Erosive Esophagitis

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.

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 Patients with Hepatic Impairment: Treatment of *H. pylori* Infection

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

Administration Instructions

- Take VONOPRAZAN with or without food.
- Swallow VONOPRAZAN tablets whole; do not chew or crush the tablet.

Missed doses:

- For the healing or maintenance of healed erosive esophagitis: If a dose is missed, administer VONOPRAZAN as soon as possible within 12 hours after the missed dose. If more than 12 hours have passed, skip the missed dose and administer the next dose at the regularly scheduled time.
- For the treatment of *H. pylori* infection: If a dose is missed, administer VONOPRAZAN as soon as possible within 4 hours after the missed dose. If more than 4 hours have passed, skip the missed dose and administer

the next dose at the regularly scheduled time. Continue the normal dosing schedule until the treatment is completed.

4.3 Contraindications

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

Contraindication with rilpivirine-containing products; avoid atazanavir.

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 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 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 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 Interaction with other medicinal products and other forms of interaction

Table 8 and Table 9 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 8: 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	
	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.	

Table 9: 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 Specific Populations

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of vonoprazan in pregnant women. Available data from pharmacovigilance reports with vonoprazan-containing products use in pregnant women are not sufficient to evaluate for a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

In pregnant rats, no adverse effects were noted after oral administration of vonoprazan during organogenesis at approximately 27-times the maximum recommended human dose (MRHD) based on AUC exposure comparisons.

In a pre- and postnatal development (PPND) study, pups from dams orally administered vonoprazan during organogenesis and through lactation, exhibited liver discoloration, which in follow-up mechanistic animal studies was associated with necrosis, fibrosis, and hemorrhage at a dose exposure during lactation. These effects were not observed at the next lower dose in this study, which was approximately equal to the MRHD based on AUC comparison, however they were seen at clinically relevant exposures in dose range finding studies in rats *(see Data)*.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Report pregnancies to the Phathom Pharmaceuticals, Inc. Adverse Event reporting line at 1-888-7757428.

Data

Animal Data

Pregnant rats were orally administered vonoprazan at doses of 30, 100, or 300 mg/kg/day (7-, 27-, 130-times the MRHD based on AUC comparison at the same doses from unmated female rats from separate studies) during the period of organogenesis from gestation day (GD) 6 to 17. During maternal dosing, one high-dose female died and decreased body weight and food consumption occurred at the middle and highest doses. No embryo-fetal lethality was observed but decreased fetal body weight was observed in the highest dose group. Fetal abnormalities were limited to the 300 mg/kg/day and included ventricular septal defect and mal-positioned subclavian artery in fetuses in a majority (15/19) of litters, as well as tail abnormalities and small anal opening. No adverse embryo-fetal effects were observed at the 100 mg/kg/day.

Pregnant rabbits were orally administered vonoprazan at doses of 3, 10, or 30 mg/kg/day (0.04-, 1.5-, 10-times the MRHD based on AUC comparison) during the period of organogenesis from GD 6 to 18. Two animals aborted at the highest dose and decreased body weight and food consumption occurred at the mid and high doses. No embryo-fetal mortality or toxicity occurred. There were no external, visceral or skeletal abnormalities.

In a PPND study, pregnant female rats were orally administered vonoprazan at doses of 1, 3, 10, or 100 mg/kg/day (0.01-, 0.18-, 1.1-, 22-times the MRHD based on AUC comparison) from GD 6 to lactation day (LD) 21. Decreased body weight gain and food consumption were present in dams at the highest dose during lactation. Decreased body weight gain compared to controls was observed in the offspring from dams in the high dose group. Liver discoloration occurred in offspring from the high dose group at LD 4 but was not present in animals examined after weaning. Similarly, in dose range finding studies in rats and follow-up mechanistic animal studies, the liver discoloration was observed and characterized as necrosis, fibrosis, and hemorrhage at equal to or greater than clinically relevant exposures based on AUC comparisons. The mechanistic studies further demonstrated the effect was likely attributable to vonoprazan exposure during lactation. The clinical relevance of the liver findings is uncertain.

Exposure margins from vonoprazan between the animal and clinical studies for vonoprazan, amoxicillin and clarithromycin used in combination may be lower due to increased vonoprazan exposure from concomitant use with clarithromycin in patients.

Lactation

Risk Summary

There are no data regarding the presence of vonoprazan in human milk, the effects on the breastfed infant, or the effects on milk production. Vonoprazan and its metabolites are present in rat milk. Liver injury occurred in offspring from pregnant and lactating rats administered oral vonoprazan at AUC exposures approximately equal to and greater than the MRHD *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential risk of adverse liver effects shown in animal studies with vonoprazan, advise patients not to breastfeed during treatment with VONOPRAZAN.

Data

Animal Data

In a PPND study in rats, in which the dams were administered oral vonoprazan during gestation and through lactation at up to 22-times the MRHD (based on AUC comparison), liver discoloration occurred in offspring from the high dose group.

Liver discoloration associated with necrosis, fibrosis, and hemorrhage in the offspring of dosed rats was also seen in dose-range finding studies and follow-up, mechanistic studies, including offspring in lactation only studies. These effects were reported in pups on LD 4 at doses from 3 to 100 mg/kg/day (approximately 0.2- to 22-fold the MRHD based on AUC values extrapolated from the PPND study) and on LD 14 at doses from

10 to 100 mg/kg/day dose groups (approximately 1- to 22-fold the MRHD based on an extrapolated AUC comparisons). In mechanistic studies, liver effects were observed in offspring treated only during lactation but not in offspring from animals only treated during gestation. In some of these studies, this finding was associated with increased offspring stomach weights that was reversed along with liver discoloration by concomitant treatment with a gastrointestinal prokinetic agent.

Pediatric Use

The safety and effectiveness of VONOPRAZAN have not been established in pediatric patients.

Geriatric Use

There were 200 patients aged 65 years and older in the clinical trial for erosive esophagitis and relief of heartburn. Of the total number of vonoprazan-treated patients there were 93 (18%) patients aged 65 years of age and older and 10 (2%) patients aged 75 years of age and older.

There were 218 patients aged 65 years and older in the clinical trial for the treatment of *H. pylori* infection. Of the total number of vonoprazan-treated patients, there were 153 (22%) patients aged 65 years of age and older and 18 (3%) patients aged 75 years of age and older.

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 for the healing of erosive esophagitis 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 for the maintenance of healed erosive esophagitis 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 < 30 mL/min).

Hepatic Impairment

Healing of Erosive Esophagitis

No dosage adjustment of VONOPRAZAN for the healing of erosive esophagitis 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 for the treatment of *H. pylori* infection in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8 Undesirable effects

The following serious adverse reactions are described elsewhere in labeling:

- Acute Tubulointerstitial Nephritis
- *Clostridioides difficile*-Associated Diarrhea
- 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 Table 5.

Table 5: 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 DailyN=514 %	Lansoprazole 30 mg Once DailyN=510 %
Gastritisc	3	2
Diarrheac	2	3
Abdominal distension	2	1
Abdominal painc	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 Table 6.

Table 6: Adverse Reactions[a] in a Clinical Trial of Adult Patients with All Grades of Erosive Esophagitis[b] (24 Week Maintenance Phase)

Adverse Reactions	VONOPRAZAN 10 mg Once DailyN=296 %	Lansoprazole 15 mg Once DailyN=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.

COVID-19

COVID-19 was reported in the healing phase in 11 (2%) VONOPRAZAN-treated subjects and 9 (2%) lansoprazole-treated subjects; and in the maintenance phase in 18 (6%) VONOPRAZAN-treated subjects and 20 (7%) lansoprazole-treated subjects.

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 two 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, urticaria

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 treatmentnaïve *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 Table 7.

Table 7: Adverse Reactions[a] in Adult Patients with *H. pylori* Infection[b]

Adverse Reactions	VONOPRAZAN and Amoxicillin N=348 %	VONOPRAZAN, Amoxicillin, and Clarithromycin N=346 %	Lansoprazole, Amoxicillin, and 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
Other adverse reactions reported in less than 2% of patients treated with VONOPRAZAN, amoxicillin, and clarithromycin or VONOPRAZAN and amoxicillin are listed below by body system:
Blood and lymphatic system disorders: anemia, leukocytosis, leukopenia, neutropenia
Cardiac disorders: QT prolongation, tachycardia
Eye 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
General disorders and administration site conditions: fatigue, pyrexia
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: ageusia, dizziness, tension headache
Psychiatric disorders: anxiety, depression, insomnia
Renal and urinary disorders: renal hypertrophy, tubulointerstitial nephritis
Reproductive system and breast disorders: vaginal discharge
Respiratory, thoracic and mediastinal disorders: cough, nasal polyps, oropharyngeal pain
Skin and subcutaneous tissue disorders: dermatitis, dry skin, rash for more information on adverse reactions and laboratory changes with amoxicillin or clarithromycin, refer to Adverse Reactions section of the corresponding prescribing information.

Postmarketing 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 suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action

Vonoprazan suppresses 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. Vonoprazan 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.

Pharmacodynamics

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 Table 10.

Table 10: Effect of VONOPRAZAN 10 mg or 20 mg Once Daily on 24-Hour Intragastric 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)		
	Baseline	Day 1	Day 7	Baseline	Day 1	Day 7
Mean Intragastric pH	2.0	3.7	4.6	1.9	4.5	5.9
% Time Intragastric 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 Intragastric 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.

5.2 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 Table 11.

Table 11: 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 (hr*ng/mL)	92.9 (33.1)[a]	230.9 (41.3)[a]	272.5 (30.5)[b]
$t_{1/2z}$ (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 AUC0-24h

b AUC0-12h

Cmax = Maximum plasma concentration; AUC0-24h = Area under the plasma concentration-time curve from time 0 to end of the 24-hour dosing interval; AUC0-12h = Area under the plasma concentration-time curve from time 0 to the end of the 12hour dosing interval; Tmax = Time to reach Cmax, t1/2 = Elimination half-life, CL/F = Apparent oral clearance, Vz/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, Cmax 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 (AUC0-12h = 273 hr*ng/mL, N=10) was approximately 1.8-fold higher compared to the mean estimate from the same subjects on Day 1 (AUC0-12h = 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 Cmax, a 15% increase in AUC, and a delay in median Tmax 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.

Elimination

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 radiolabeled dose (8% as unchanged vonoprazan) was recovered in urine and 31% (1.4% as unchanged vonoprazan) was recovered in feces.

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

Sex, Race or Ethnicity
There were no clinically significant differences in the pharmacokinetics of vonoprazan based on sex or race/ethnicity.

Patients with Renal impairment
The pharmacokinetics of vonoprazan administered as a single 20 mg dose in patients with mild [eGFR 60 to <90 mL/min/1.73m^2 (N=8)], moderate [eGFR 30 to <60 mL/min/1.73m^2 (N=8)], or severe [eGFR 15 to <30 mL/min/1.73m^2 (N=8)] renal impairment were compared to those with normal renal function [eGFR ≥90 mL/min/1.73m^2 (N=13)]. Compared to subjects with normal renal function, systemic exposure (AUC0-inf) was 1.7-, 1.3-, and 2.4-times greater in patients with mild, moderate, and severe renal impairment, respectively. In subjects requiring dialysis (N=8), AUC0-inf estimates were 1.3-fold greater compared to estimates from subjects with normal renal function. Protein binding of vonoprazan is not affected by impaired renal function. In patients requiring dialysis, vonoprazan was present in the dialysate and represented 0.94% of the dose administered.

Patients with Hepatic Impairment
The pharmacokinetics of vonoprazan administered as a single 20 mg dose in patients with mild [Child-Pugh Class A (N=8)], moderate [Child-Pugh Class B (N=8)], or severe [Child-Pugh Class C (N=6)] hepatic impairment were compared to those with normal hepatic function (N=12). Compared to subjects with normal hepatic function, systemic exposure (AUC0-inf) of vonoprazan was 1.2-, 2.4-, and 2.6-times greater in patients with mild, moderate, and severe hepatic impairment, respectively. Protein binding of vonoprazan is not affected by impaired hepatic function.

5.3 Preclinical safety data
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity
In a 24-month carcinogenicity study in mice, vonoprazan at daily oral doses of 6, 20, 60, and 200 mg/kg/day (approximately 0.4-, 4-, 19-, and 93-times the MRHD based on AUC) produced hyperplasia of neuroendocrine cells, gastropathy and benign and/or malignant neuroendocrine cell tumors (carcinoids) in the stomach at all doses in males and at 60 mg/kg/day and greater in females. In liver, increased incidences of hepatocellular adenoma and carcinomas were observed at doses of 20 mg/kg/day and greater in males and 60 mg/kg/day and greater in females.
In a 24-month carcinogenicity study in Sprague-Dawley rats, vonoprazan at daily oral doses of 5, 15, 50, and 150 mg/kg/day (approximately 0.6-, 4-, 19-, and 65-times the MRHD based on AUC) produced benign and/or malignant neuroendocrine cell tumors in the stomach in both male and female rats at doses of 5 mg/kg/day or more. Increased incidence of hepatocellular adenoma and carcinomas and hepatocholangiocellular adenomas and carcinomas were observed at doses of 50 and 150 mg/kg/day.
In both mice and rats, neuroendocrine tumors in the stomach occurred in association with neuroendocrine hyperplasia and gastropathy in the stomach and increased plasma gastrin concentrations that are consistent

with inhibition of gastric acid secretion. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with proton pump inhibitors or high doses of H_2-receptor antagonists.

Mutagenesis

Vonoprazan was negative for mutagenicity in the *in vitro* Ames test, in an *in vitro* clastogenecity assay in Chinese Hamster cells and *in vivo* in a rat bone marrow micronucleus study.

Impairment of Fertility

Vonoprazan at oral doses up to 300 mg/kg/day in rats (approximately 133-times the MRHD based on AUC from a separate study in nonpregnant animals administered the same dose) was found to have no effect on fertility and reproductive performance. Elongation of the estrous cycle was observed in rats at doses equivalent to 133-times the MRHD based on AUC.

Animal Toxicology and/or Pharmacology

During lifetime exposure of mice and rats dosed daily with up to 200 mg/kg/day and 150 mg/kg/day of vonoprazan respectively, increases in gastrin levels and marked neuroendocrine hyperplasia and gastropathy were observed followed by formation of carcinoid tumors. This finding is considered to be a rodent-specific phenomenon.

6. Pharmaceutical particulars

6.1 List of excipients

Core tablet: Mannitol, Microcrystalline cellulose-102, Fumaric Acid, Hydroxy Propyl Cellulose, Sodium Lauryl Sulphate, Purified Talc & Magnesium Stearate.

Coating Material: Hypromellose (E-15), Purified Talc, Titanium Dioxide, Polyethylene Glycol (As 6000), Col. Ferric Oxide Red, Iso Propyl Alcohol and Dichloromethane.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 Tablets are packed in Alu- Alu blister and 3 such Alu-Alu blisters are packed in carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Galaxy Pharmaceutical Ltd.
Plot No 20263, Off Old Mombasa Road,
PO Box 39107-00623, Nairobi, Kenya.

Manufacturer

Saitech Medicare Pvt. Ltd.
Trilokpur road, Kala-Amb
Dist. Sirmor, Himachal Pradesh (INDIA).

8. Marketing Authorization Number

CTD13165

9. Date of first <Registration> / Renewal of the <Registration>

14/07/2026

10. Date of revision of the text

14/07/2026