SUMMARY OF PRODUCT CHARECTERSTICS

1. NAME OF THE MEDICINAL PRODUCT

VONACID – 10 (Vonoprazan Tablets 10 mg)
VONACID – 20 (Vonoprazan Tablets 20 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION VONACID – 10:

Each film coated tablet contains:
Vonoprazan fumarate equivalent to Vonoprazan ----------10 mg

VONACID – 20:
Each film coated tablet contains:
Vonoprazan fumarate equivalent to Vonoprazan ----------20 mg

3. PHARMACEUTICAL FORM

Tablets, 10 mg & 20 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

- Vonoprazan is indicated: 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
Recommended Dosage
<u>Healing of Erosive Esophagitis and Relief of Heartburn</u>

- The recommended adult oral dosage is Vonoprazan 20 mg once daily for 8 weeks.

<u>Maintenance of Healed Erosive Esophagitis and Relief of Heartburn</u>

- The recommended adult oral dosage is Vonoprazan 10 mg once daily for up to 6 months.

<u>Treatment of H. pylori Infection</u>

- 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 Sections or subsections omitted from the full prescribing information are not listed. 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 8 below.

Table 8: 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 9 below.

Table 9: Recommended Vonoprazan Dosage in Patients with Renal Impairment: Treatment of H. pylori Infection

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

*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 10 below.

Table 10: 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 11 below.

Table 11: Recommended Vonoprazan Dosage in Patients with Hepatic Impairment: Treatment of H. pylori Infection

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

Administration

- 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.
- Vonoprazan is contraindicated with rilpivirine-containing products.
- For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with Vonoprazan.

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.

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 atrisk 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 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

<table>
<tr><td colspan="3">Drugs Dependent on Gastric pH for Absorption</td></tr>
<tr><td colspan="3">Antiretrovirals</td></tr>
<tr><td>Clinical Effect</td><td colspan="2">Vonoprazan reduces intragastric acidity which may alter the absorption of antiretroviral drugs leading to changes in the safety and/or effectiveness.</td></tr>
<tr><td>Prevention or Management</td><td>Rilpivirine-containing products</td><td>Concomitant use with Vonoprazan is contraindicated.</td></tr>
<tr><td></td><td>Atazanavir</td><td rowspan="2">Avoid concomitant use with Vonoprazan</td></tr>
<tr><td></td><td>Nelfinavir</td></tr>
<tr><td></td><td>Other antiretrovirals</td><td>See the prescribing information of other antiretroviral drugs dependent on gastric pH for absorption prior to concomitant use with Vonoprazan.</td></tr>
<tr><td colspan="3">Other Drugs (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)</td></tr>
</table>

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 antiplatelet 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 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 Pregnancy and lactation

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.

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. 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.

4.7 Effects on ability to drive and use machines
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.

4.8 Undesirable effects
None stated.

4.9 The over dosage
None stated.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties:
Pharmacotherapeutic group: potassium-competitive acid blocker. ATC code: A02BC08

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.

5.2 Pharmacokinetic properties

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 ($AUC_{0\text{-}inf}$) 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), $AUC_{0\text{-}inf}$ 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 ($AUC_{0\text{-}inf}$) 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.

Drug Interaction Studies

In Vitro Studies

Cytochrome P450 (CYP450) Enzymes

In vitro studies have shown that vonoprazan directly and time-dependently inhibits CYP2B6, CYP2C19, and CYP3A4/5.

Transporter Systems

Vonoprazan inhibits multidrug and toxin extrusion protein 1 (MATE1) and organic cation transporter 1 (OCT1), but only at concentrations higher than clinically relevant.

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 euroendocrine 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

Vonoprazan - 10

Mannitol, Microcrystalline cellulose, Hydroxypropyl cellulose, Fumaric acid, Purified water, Croscarmellose sodium, Magnesium stearate, Instacoat Universal Yellow (A05D05501)

Vonoprazan - 20

Mannitol, Microcrystalline cellulose, Hydroxypropyl cellulose, Fumaric acid, Purified water, Croscarmellose sodium, Magnesium stearate, Instacoat Universal pink (A05D05500)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months from the date of manufacture

6.4 Special precautions for storage

Do not store above 30^0C. Keep out of the reach and sight of children.

6.5 Nature and contents of container
Alu-Alu blister packs of 10's

6.6 Special precautions for disposal and other handling
None

7. Applicant:

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