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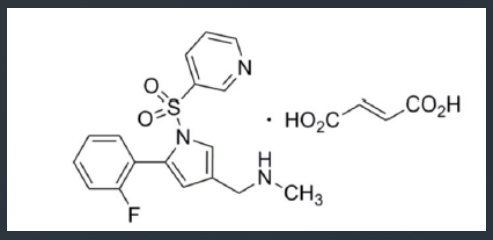

Dr. M. Solduzian

Pharm D BCPS

vonoprazan

PRESCRIBING

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INDICATIONS AND USAGE

- 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.

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DOSAGE AND ADMINISTRATION

- Healing of Erosive Esophagitis and Relief of Heartburn
  - • The recommended adult oral dosage is VOQUEZNA 20 mg once daily for 8 weeks.
- Maintenance of Healed Erosive Esophagitis and Relief of Heartburn
  - • The recommended adult oral dosage is VOQUEZNA 10 mg once daily for up to 6 months.
- Treatment of *H. pylori* Infection
  - Triple Therapy: The recommended adult oral dosage is VOQUEZNA 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.

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Recommended 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

- **Recommended VOQUEZNA Dosage in Patients with Renal**

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

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Recommended Dosage in Patients with Hepatic Impairment

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

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

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Administration Instructions

- Take VOQUEZNA with or without food
- Missed doses:
  - For the healing or maintenance of healed erosive esophagitis: If a dose is missed, administer VOQUEZNA 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 VOQUEZNA 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

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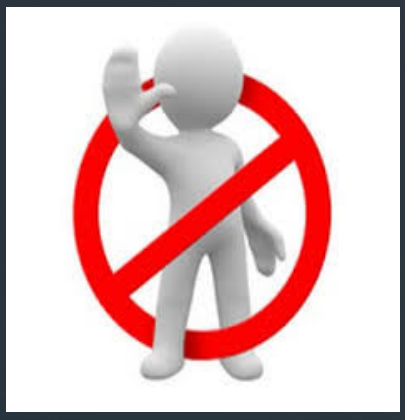
CONTRAINDICATIONS

- Known hypersensitivity to vonoprazan or any component of the formulation
- With rilpivirine-containing products



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WARNINGS AND PRECAUTIONS

- **Presence of Gastric Malignancy**
- **Acute Tubulointerstitial Nephritis**
- ***Clostridioides difficile*-Associated Diarrhea**
- **Bone Fracture**
- **Severe Cutaneous Adverse Reactions**
- **Vitamin B12 (Cobalamin) Deficiency**
- **Hypomagnesemia and Mineral Metabolism**

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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 VOQUEZNA treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.

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Fundic Gland Polyps

- Use of VOQUEZNA 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 VOQUEZNA appropriate to the condition being treated

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ADVERSE REACTIONS

- Adverse Reactionsa in a Clinical Trial of Adult Patients with All Grades of Erosive Esophagitisb (2 to 8 Week Healing

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

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

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ADVERSE REACTIONS

- Adverse Reactionsa in a Clinical Trial of Adult Patients with All Grades of Erosive Esophagitisb (24 Week Maintenance Phase)

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

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

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ADVERSE REACTIONS

- **Adverse Reactionsa in Adult Patients with *H. pylori* Infectionb**

Adverse Reactions	VOQUEZNA and Amoxicillin N=348 %	VOQUEZNA, 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.

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DRUG INTERACTIONS

Drugs Dependent on Gastric pH for Absorption		
Antiretrovirals		
Clinical Effect	Vonoprazan reduces intragastric acidity *[see Clinical Pharmacology (12.2)]* 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 VOQUEZNA is contraindicated.
	Atazanavir	Avoid concomitant use with VOQUEZNA.
Other Drugs (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)		
Clinical Effect	Vonoprazan reduces intragastric acidity *[see Clinical Pharmacology (12.2)]*, 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.	

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DRUG INTERACTIONS

Certain CYP3A Substrates where minimal concentration changes may lead to serious toxicities		
Clinical Effect	Vonoprazan is a weak CYP3A inhibitor *[see Clinical Pharmacology (12.3)]*. 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 VOQUEZNA. 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 *[see Clinical Pharmacology (12.3)]*. 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.

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DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inducers	
Clinical Effect	Vonoprazan is a CYP3A substrate. Strong or moderate CYP3A inducers decrease vonoprazan exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the effectiveness of VOQUEZNA.
Prevention or Management	Avoid concomitant use with VOQUEZNA.

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USE IN SPECIFIC POPULATIONS

- **Pregnancy**
- 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.

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USE IN SPECIFIC POPULATIONS

- **Lactation**
  - 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 VOQUEZNA.

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USE IN SPECIFIC POPULATIONS

- **Pediatric Use**
  - The safety and effectiveness of VOQUEZNA have not been established in pediatric patients.
- **Geriatric Use**
  - No overall differences in safety or effectiveness were observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between the geriatric and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

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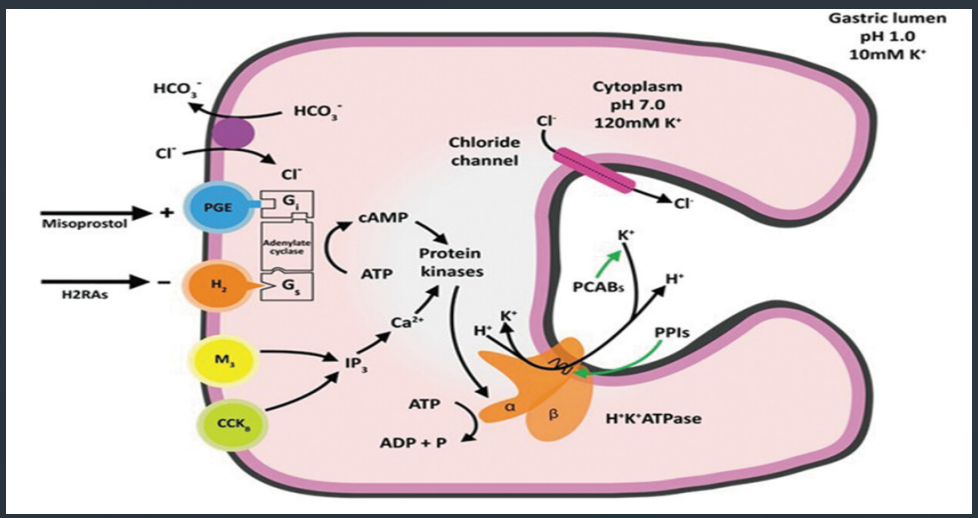
Mechanism of Action



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Pharmacodynamics

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

Parameter	VOQUEZNA 10 mg Once Daily (N=9)			VOQUEZNA 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)

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Pharmacokinetics

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] $AUC_{0\text{-}24h}$
[b] $AUC_{0\text{-}12h}$

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