Vonoprazan (VOQUEZNA)
in Erosive Esophagitis
National Drug Monograph
May 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 1L, first-line; 2L, second-line; %p, percentage point(s); ARD, absolute risk difference; CO, crossover; DB, double-blind; DD, double-dummy; ER, extended release; ESO, esomeprazole; FAS, full analysis set; ITT, intent-to-treat; LA-C/D, Los Angeles Classification of Gastroesophageal Reflux Disease Grade C/D (scale: A / mild to D / severe); LAN, lansoprazole; MC, multicenter; mITT, modified intent-to-treat; MN, multinational; MTZ, metronidazole; nbPU, nonbleeding peptic ulcer; NI, noninferior(ity); OL, open-label; Ph2/3/4, phase 2/3/4; PP, per protocol; RAB, rabeprazole; RUT, rapid urease test; SAT, stool *H. pylori* antigen test; SB, single-blind; SC, single-center; SSD, statistically significant difference; UBT, urea breath test; VACHCS, Veterans Affairs Connecticut Healthcare System; VON, vonoprazan

FDA Approval Information

Description / Mechanism of Action

- First-in-class potassium-competitive acid blocker (PCAB). Vonoprazan binds reversibly to potassium ions on potassium channels adjacent to the gastric H+, K+-ATPase proton pump in the parietal cell and inhibits the final step of acid production.[1]
- In contrast to proton pump inhibitors, vonoprazan binds ionically (reversibly) rather than covalently, binds to active and inactive pumps (can be taken without regard to meals), does not require activation to an active moiety by acid, is acid stable, has a faster onset of acid suppressive effects (one dose vs 3–5 days),[2] has a longer duration of action, and is not subject to variable effects due to CYP2C19 polymorphisms.[3]
- It is the first new gastric acid antisecretory agent approved in the US in 30 years. The FDA granted fast-track status to vonoprazan copackaged with antibiotics for the treatment of *H. pylori* infection in 2019. The individual vonoprazan product was approved for erosive esophagitis (EE) in November 2023.
- Vonoprazan has been approved in Japan since 2015 and is approved in 14 Asian or South American countries or territories.

Indications Under Review in This Document

- Healing of all grades of EE and relief of heartburn associated with EE in adults.
- Maintenance of healing of all grades of EE and relief of heartburn associated with EE in adults.

Dosage Regimen

Table 1 Standard Dosage

Indication	Recommended Dosage
Healing of Erosive Esophagitis and Relief of Heartburn	20 mg once daily for 8 weeks
Maintenance of Healed Erosive Esophagitis and Relief of Heartburn	10 mg once daily for up to 6 months

Table 2 Dosage Modification for Renal Impairment

Indication	Estimated GFR	Recommended Dosage
Healing of Erosive Esophagitis	≥ 30 mL/min	20 mg once daily
	< 30 mL/min	10 mg once daily
Maintenance of Healed Erosive Esophagitis	—	Same as for normal renal function

Table 3 Dosage Modification for Hepatic Impairment

Indication	Child-Pugh Class	Recommended Dosage
Healing of Erosive Esophagitis	A	20 mg once daily
	B and C	10 mg once daily
Maintenance of Healed Erosive Esophagitis	—	Same as for normal hepatic function

Dosage Forms and Packaging Under Review

- Tablets in bottles of 30: 10 mg and 20 mg

Efficacy Considerations

- Six active-controlled randomized clinical trials (RCTs) have been published including the PHALCON-EE trial conducted in Western countries (US and EU)[10] (Table 4). Four of these trials tested for noninferiority.[10,11,12,15]
- There were five Asian trials,[11,12,13,14,15] the results of which may not be generalizable to Western populations because of differences in patient factors that may affect the extent of acid suppression.
- A single, small RCT that evaluated vonoprazan in a "PPI-resistant" population who had tried standard or higher doses of PPIs / lansoprazole suggested that switching to the PCAB resulted in additional healing of EE and improvement in gastric pH control (Table 5).[16] Small, prospective, single-arm, observational studies of vonoprazan in patients with PPI-refractory EE suggested that switching to vonoprazan improved esophageal acid exposure, symptom control and esophagitis healing.[4,5,6,7,8,9]
- The evidence reviewed below focuses on clinical outcomes (healing of EE) rather than pH control since differences in pH control do not necessarily translate to clinical benefits.

Table 4 Summary of RCTs in EE (LA Grades A–D)

Reference, Country	Study Design	Major Entry Criteria	Interventions in mg (N)	Main Efficacy Results (mITT)		ARD (95% CI)	Q
Healing and Maintenance Trials							
Laine (2023; VACHCS),[10] US and EU Authors have COI with Phathom	PHALCON-EE: MN DB NI registration RCT, healing and rerandomized maintenance NI margin of 10% ~30% LA-C/D EE Multiplicity controlled by fixed sequence analysis Stratified by LA Grade of EE	<u>Healing Phase</u> EE on blinded, centrally read endoscopy, *H. pylori*-negative, no Barrett's esophagus	<u>8-wk treatment</u> VON 20 QD (514) LAN 30 QD (510)	NI in healing rate by Wk 8 (mITT, PP) 478/514 (92.9%) 431/510 (84.6%) Greater tx effect in LA-C/D subgroup: Healing rate by Wk 8 (exploratory) VON: 162/177 (91.7%) LAN: 125/174 (72.0%)	RR 1.1 (1.05, 1.15) RR 1.3 (1.15, 1.41)	8.3 (4.5, 12.2) Ref 19.6 (11.8, 27.6) Ref	High
		<u>Maintenance</u> Endoscopically healed at Wk 2 or Wk 8	<u>24-wk treatment</u> VON 20 QD (293) VON 10 QD (291) LAN 15 QD (294)	NI and SSD in maintenance of healing at Wk 24 (mITT, PP): 235/291 (80.7%) 232/293 (79.2%) 212/294 (72.0%) SSD between both VON doses vs LAN in maintenance of healing at Wk 24 in LA-C/D subgroup (predefined): VON20: 71/92 (77.2%) VON10: 71/95 (74.7%) LAN15: 59/96 (61.5%)	 RR 1.1 (1.02, 1.23) RR 1.1 (1.00, 1.20) RR 1.3 (1.03, 1.52) RR 1.2 (1.00, 1.48)	 8.7 (1.8, 15.5) 7.2 (0.2, 14.1) Ref 15.7 (2.5, 28.4) 13.3 (0.02, 26.1) Ref	
Ashida (2016),[11] Japan	Pivotal MC DB NI RCT (healing) MC SB RCT (rerandomized maintenance)	<u>Healing Phase</u> EE on endoscopy <u>Maintenance</u> Endoscopically healed at Wk 2, 4, or 8	<u>8-wk treatment</u> VON 20 QD (207) LAN 30 QD (202) <u>52-wk treatment</u> VON 10 QD (151) VON 20 QD (154)	NI and post hoc SSD in healing rate up to Wk 8 203/205 (99.0%) 190/199 (95.5%) EE recurrence by endoscopy at Wk 52: 14/149 (9.4%) 13/145 (9.0%)	 RR 1.0 (1.00, 1.07) RR 1.0 (0.51, 2.15)	 3.5 (0.36, 6.73) Ref 0.4 (–6.2, 7.0) Ref	High
Healing Trials							
Xiao (2019),[12] Asia	Ph3 MN DB DD NI RCT, healing NI margin, ≥ –10%	<u>Healing Trial</u> EE on endoscopy	<u>8-wk treatment</u> VON 20 QD (244) LAN 30 QD (235)	NI in healing rate at Wk 8 203/220 (92.4%) 192/210 (91.3%)	 RR 1.0 (0.95, 1.07)	 1.1 (–3.82, 6.09) Ref	Moderate[α]
Oshima (2019),[13] Japan	SC DB RCT	EE on endoscopy with recent h/o at least weekly severe or very severe heartburn episodes (score ≥ 2 on a Likert scale of 0–4)	<u>2-wk treatment</u> VON 20 QD (16) LAN 30 QD (16)	Complete heartburn relief on days 1–7: 65% 25% Values estimated from Figure 2 of article. Data not reported clearly.		—	Unable to assess

Reference, Country	Study Design	Major Entry Criteria	Interventions in mg (N)	Main Efficacy Results (mITT)	ARD (95% CI)	Q
Maintenance Trials						
Matsuda (2022),[14] Japan	MC OL CO RCT No washout period. Effects of first drug were expected to be gone by 1 wk after CO.	EE GERD on endoscopy; responded to PPI and receiving maintenance PPI therapy	Given Q2D: **VON-LAN**: VON 10 x 4 wks then LAN 15 x 4 wks (63) **LAN-VON**: Reverse order (59)	NSD between VON and LAN in rate of asymptomatic patients: 67/112 (59.8%) vs 61/112 (54.5%), respectively. SSD in rate of well-controlled patients: **Vonoprazan** / **Lansoprazole** Well-controlled / **Lansoprazole** Symptomatic Well-controlled 89 16 Symptomatic 3 4 McNemar's test 0.003. N = 112.	–0.05 (–0.18, 0.08) —	Very low[β]
Ashida (2018),[15] Japan	Ph2 MC DB DD NI RCT	Recurrence of EE on endoscopy after 8-wk treatment with VON 20 mg QD	24-wk treatment VON 10 QD (202) VON 20 QD (204) LAN 15 QD (201)	NI and SSD (post hoc) in EE recurrence at Wk 24: 10/197 (5.1%) RR 0.3 (0.15, 0.59) 4/201 (2.0%) RR 0.1 (0.04, 0.33) 33/196 (16.8%) Ref 95% CI contained the value 0 for VON10 vs VON20	–11.8 (–17.8, –5.7) –14.8 (–9.3, –20.4) Ref	Moderate[γ]

Q, GRADE (Grading of Recommendations, Assessment, Development and Evaluation) quality of evidence rating

[α] Downgraded for indirectness (Asian population may differ from Western populations in acid suppression)

[β] Downgraded for risk of bias (not blinded), indirectness of outcome measure and imprecision (optimal information size not met)

[γ] Downgraded for imprecision (optimal information size not met)

Table 5 Summary of Dose-controlled RCT in "PPI-resistant" EE

Reference, Country	Study Design	Major Entry Criteria	Interventions in mg (N)	Main Efficacy Result(s) (mITT)	ARD (95% CI)	Q
Iwakiri, et al. (2017),[16] Japan	MC DB RCT Pts with baseline EE of grade 0 as assessed by a central adjudication committee were excluded (unplanned). Limitation: A 14-d run-in trial of LAN 30 may be insufficient.	At least standard doses of PPIs for ≥ 8 wks before the run-in period; PPI-resistant EE (confirmed by endoscopy) despite prior PPI and run-in LAN therapy; no esophageal complications other than Schatzki's ring and Barrett's esophagus	7–14-d Run-in Period LAN 30 QD 8-wk treatment VON 40 QD (10) VON 20 QD (9)	Endoscopic healing rate after Wk 8: VON40: 5/7 (71.4%) RR 1.2 (0.51, 2.80) VON20: 3/5 (60.0%) NSD in absolute CFB in 24-h gastric pH 4 holding time ratio at Wk 2: VON40: 70%→100%; CFB, 30%p (12.2, 47.1) VON20: 73%→96%; CFB 23%p (5.4, 41.1)	11.4 (–0.43, 0.66)	Very low[α]

[α] Downgraded for risk of bias (randomization, blinding, and allocation methods were not reported), indirectness (Asian vs Western population; patients identified as PPI-resistant without necessarily receiving a trial of double-dose PPIs; LAN 30 QD is a standard dose in US; VON vs PPI comparator), and imprecision (suboptimal information size); also lack of placebo or PPI control

Network Meta-analyses

Table 6 Summary of Network Meta-analyses Comparing Therapies for EE / GERD

Reference	K (N)	Outcome	Ranked Best	Ranked Worst	Vonoprazan Better Than	Vonoprazan Similar to	Vonoprazan Worse Than
Heartburn Symptoms in EE							
Oshima (2022)[17]	10 (NR; 32–5241 per RCT) VON: 1 (32)	Heartburn resolution on (1) D1 and (2) D7	VON20 for both outcomes	OME20	—	D1 ESO20BID/40/20 LAN30 PAN40 OME20 D7 RAB20 ESO20BID/40/20 LAN30 PAN40 OME20	—
Healing of EE							
Yang (2022)[18]	41 (11,592) VON: 4 (1374)	Mucosal healing of EE at 4 wks†	ESO	RAB	—	OME LAN PAN RAB ESO	—
Healing of Grade C/D EE							
Zhuang (2024)[19]	13 (9267) for initial treatment	Failure in healing at 8 wks	VON20	OME20	LAN30 OME20	DEX60 ESO40 RAB ER 50 PAN40 ESO20	—
	4 (1834) for maintenance treatment	Failure in heaing at 24 wks	LAN30 VON20	PAN20	PPIs RAB10 LAN15 ESO10 OME10	LAN30 ESO20 LAN15 PAN20	—
Maintenance Treatment of GERD							
Miwa (2019)[20]	23 (NR) VON: 1 abstract (594)	Maintained endoscopic remission or endoscopic remission rate at 6 mos	SUCRA not done	SUCRA not done	VON10 ESO10 OME10 VON20 ESO10 RAB10 LAN15 OME10	VON10 RAB10 LAN15	—
Adverse Events							
Yang (2022)[18]	Same as Yang (2022) above	AE rate	OME	VON	—	OME LAN PAN RAB ESO	—

Table includes FDA-approved drugs only. None of the network meta-analyses included the PHALCON-EE trial of vonoprazan (reference 10).
SUCRA, surface under the cumulative ranking score
† Results at 8 wks were the same as those for 4 wks.

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings**: None
- **Contraindications**: Hypersensitivity; rilpivirine-containing products.
- **Other Warnings / Precautions**: Presence of gastric malignancy (despite symptomatic response to treatment); acute tubulointerstitial nephritis; *Clostridioides difficile*-associated diarrhea (CDAD); bone fracture; severe cutaneous adverse reactions; vitamin B12 / cobalamin deficiency; hypomagnesemia and mineral metabolism; interactions with diagnostic investigations for neuroendocrine tumors; fundic gland polyps (particularly with therapy beyond 1 year)
- **Common Adverse Events** (≥ 2%–3%)
    - **EE, Healing Phase (2–8 Weeks):** Gastritis, diarrhea, abdominal distension, abdominal pain; nausea
    - **EE, Maintenance Phase (24 Weeks):** Gastritis, abdominal pain, dyspepsia, hypertension, urinary tract infection
- **Pregnancy:** May cause fetal harm. Patients should be counseled if they are pregnant or plan to become pregnant.
- **Lactation:** Infant risk cannot be ruled out; inconclusive or inadequate evidence. Weigh potential benefits vs risks.

Adverse Events of Special Interest

- **Liver Test Abnormalities**. Another PCAB drug has been associated with drug-related hepatic changes. ALT or AST elevations > 3 times the upper limit of normal occurred in 1 or 2 patients (0.2% to 0.4%) per treatment group in the PHALCON-EE trial.[10]

Safety Results from Clinical Trials

Adverse Events

- There is a lack of safety data beyond 3 years.
- In the 24-week maintenance phase of the PHALCON-EE trial, vonoprazan 20 mg had numerically higher rates of serious adverse events than vonoprazan 10 mg and lansoprazole 15 mg (4.7%, 3.4% and 2.4%, respectively).[10] A similar pattern was seen with discontinuations due to adverse events (2.7%, 0.7% and 0.7%, respectively) and adverse events (56.4% vs 54.1% and 50.5%, respectively). In the healing phase, the rates of adverse events and serious adverse events were comparable between vonoprazan 20 mg and lansoprazole 30 mg.
- In other PPI comparator trials, vonoprazan and PPIs were similar in adverse event rates, drug-related adverse events, discontinuations due to adverse events, and serious adverse events.[12,14,15,11]
- In the dose-controlled trial involving PPI-refractory patients, treatment-emergent adverse events occurred in 6 (60%) of 10 patients on vonoprazan 40 mg and 4 (44.4%) of 9 patients on vonoprazan 20 mg.[16]

Hypergastrinemia

- The PHALCON-EE trial showed higher serum gastrin levels on vonoprazan than lansoprazole in both the healing phase (mean, 158.3 vs 64.1 pg/mL) and maintenance phase (223, 166 and 74 pg/mL for vonoprazan 20 mg, 10 mg and lansoprazole 30 mg, respectively).[10] During maintenance, serum gastrin levels of > 500 pg/mL occurred in 16%, 11% and 1.3% of patients, respectively.[10] Serum gastrin levels

decreased to 77, 66 and 60 pg/mL four weeks after ending maintenance therapy in the vonaprazan 20 mg, 10 mg, and lansoprazole 30 mg groups, respectively.[10] These levels were higher than baseline.

Histopathologic Changes of Gastric Mucosa

- In the PHALCON-EE trial, the net increase in the percentage of patients with enterochromaffin-like (ECL) cell hyperplasia on biopsy was numerically higher with vonoprazan 20 mg relative to vonoprazan 10 mg and lansoprazole 30 mg: 13/263 (4.9%), 6/266 (2.3%) and 3/260 (1.2%), respectively.[10] The net changes in the number of patients with gastric atrophy and gastric intestinal metaplasia were small and comparable among the treatment groups.[10]
- In the 3-year interim results of VISION, a 5-year phase-4 multicenter, open-label, safety RCT conducted in Japan, 102 (93.6%) of 109 vonoprazan (10 mg) patients vs 45 (78.9%) of 57 lansoprazole (15 mg) patients had parietal cell protrusion / hyperplasia at 156 weeks.[21] G-cell hyperplasia was seen in 93 patients (85.3%) and 40 patients (70.2%) of the vonoprazan and lansoprazole groups, respectively, at Week 156. No worsening of neoplastic / dysplastic epithelial cell changes, foveolar hyperplasia, and enterochromaffin-like (ECL)-cell hyperplasia, or endocrine cell micronest were seen.

Postmarketing Safety Reports

- A case of foveolar gastric adenocarcinoma has occurred during long-term administration of vonoprazan.[22]

Evidence Gaps

- Health-related Quality of Life
- Functional ability / Disability

Other Considerations

- The safety and efficacy of vonoprazan taken daily[23,24] or on demand[25] are being evaluated in patients with nonerosive reflux disease (NERD).
- The effectiveness of vonoprazan in PPI-resistant NERD has also been described in retrospective studies.[26]

Other Therapeutic Options

Table 7 Antisecretory Treatment Options for EE

Drug / Class	On VANFI	CFU Place in Therapy	FDA Place in Therapy for EE-related Indications	ACG GERD CPG[27]	AGA GERD CPU (2022) Place in Therapy[28]	AGA EER CPU (2023) Place in Therapy[29]
PCAB						
Vonoprazan	TBD	TBD	Healing and maintenance of healing of all grades of EE and relief of heartburn related to EE in adults	Not mentioned (drug approved in 2023)		
PPIs						
Omeprazole cap EC, tab SA†	Yes	NA	Short-term (4–8 wks) treatment of EE due to endoscopically-confirmed acid-mediated GERD	Recommended for classic GERD heartburn and regurgitation without alarm symptoms (8-wk empiric trial) Recommended over H2RAs for EE healing and maintenance of healing In LA Grade C/D EE, PPI maintenance therapy should be continued indefinitely.	PPIs are 1st line	*Potential EER with typical GERD symptoms*: Reasonable to try initial single-dose PPI with up-titration to twice daily PPI for 8–12 wks. *Potential EER without typical GERD symptoms*: Consider diagnostic testing for reflux before starting PPI therapy.
Dexlansoprazole cap EC	No	NA	Healing and maintenance of all grades of EE, heartburn			
Esomeprazole	Yes (inj only†)	NA	Oral cap, susp: Short-term (4–8 wks) treatment in healing and symptomatic resolution of diagnostically confirmed EE, maintenance of healing of EE, and short-term treatment (4–8 wks) of heartburn and other symptoms associated with GERD Injection: Short-term treatment of GERD with EE as an alternative to oral therapy when oral esomeprazole is not possible or appropriate.			
Lansoprazole cap EC, ODT	No	NA	Short-term treatment and maintenance of healing and symptom relief of all grades of EE			
Pantoprazole tab	Yes	NA	Short-term treatment (up to 8 wks) and maintenance of healing and symptomatic relief of EE			
Rabeprazole cap sprinkle, tab EC	No	NA	Short-term treatment of erosive or ulcerative GERD for 4–8 wks			

CFU, criteria for Use; CPU, clinical practice update; EE, erosive esophagitis; EER, extraesophageal reflux; ODT, oral disintegrating tablet
† Other formulations are nonformulary

Projected Place in Therapy

Summary of Evidence

- Three RCTs, including the large, high-quality PHALCON-EE trial, have shown that vonoprazan 20 mg is noninferior to lansoprazole 30 mg in healing of EE.[10,11,12] Vonoprazan 10 or 20 mg has been shown to be noninferior to lansoprazole 15 mg in either maintenance of healing[10] or recurrence rates.[15] In the largest, well-designed PHALCON-EE trial conducted in the US and EU, vonoprazan was superior to lansoprazole 15 mg in maintenance of healing at Week 24 with absolute treatment differences of 7.2 and 8.7 percentage points with vonoprazan 10 mg and 20 mg, respectively (high quality evidence of small effects).[10] Results of subgroup analyses suggested that, relative to lansoprazole, vonoprazan may have a greater effect in maintenance of healing in patients with LA grade C/D EE and a similar effect in those with LA grade A/B EE.[10] It is uncertain whether the results of trials performed in Asian countries can be extrapolated to Western populations.
- There is a lack of long-term safety experience in Western populations. Potential complications of chronic hypergastrinemia of the extent and severity seen with vonoprazan are unknown. Hyperplastic changes of gastric parietal cells and G-cells are common with both vonoprazan and PPIs but may occur more frequently with vonoprazan. The prescribing information warns of fundic gland polyps most of which were found incidentally on endoscopy and advises using the shortest duration of therapy clinically required.
- No trials have evaluated vonoprazan relative to PPIs in patients with PPI-refractory EE or compared vonoprazan with escalated doses of PPIs (double-dose or twice-daily therapy).
- No trials have evaluated vonoprazan in Barrett's esophagus.
- The few network meta-analyses available were inconsistent in showing that vonoprazan was more effective than PPIs; however, they were limited by incomplete inclusion of vonoprazan trials and potential skewing of results due to inclusion of Asian studies.
- The VHA drug acquisition cost of vonoprazan is more than 800 times that of the formulary PPI omeprazole and more than 10 times the cost of dexlansoprazole, the highest-cost PPI.

Potential Place in Therapy in VHA

- Vonoprazan may be an alternative treatment for healing and maintenance of healing in patients with EE confirmed by endoscopy and, if indicated, pH monitoring who are PPI-refractory or for whom PPIs are not tolerated. PPI refractoriness is defined here as an inadequate endoscopic response or intolerance to ≥ 8-week trials of properly timed / administered double-dose or twice daily formulary PPI and properly timed / administered double-dose or twice daily esomeprazole or rabeprazole (PPIs less affected by CYP2C19 polymorphisms).

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