ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14937088

VONOPRAZAN: An Innovative Approach to Acid-Related Disorders

T. Rama Rao*[1]; D. Akshaya[1]; G. Sravya[1]; T. Kaushik[1]

[1]Department of Pharm. D, CMR College of Pharmacy, Hyderabad, India

***Corresponding Author:**
Tadikonda Rama Rao
Professor & Principal,
CMR College of Pharmacy,
Kandlakoya Village, Medchal Road,
Hyderabad – 501401,
Telangana, India.
Orcid Number: 0000-0003-1746-2167

Publication Date: 2025/02/28

Abstract: A frequent condition of the upper gastrointestinal system, gastro-esophageal reflux extermination causes the contents of the stomach to reflux into the esophagus. Less frequent reflux symptoms include heartburn, dysphagia, belching, hiccups, nausea, and vomiting.

In order to treat and prevent acid-related conditions such as erosive esophagitis, gastric ulcer, duodenal ulcer, peptic ulcer, gastro-esophageal reflux, reflux esophagitis, and Helicobacter pylori eradication, vonoprazan, an oral bioavailable P-CAB, is being developed. 10 mg and 20 mg are among the dosages. Women who are or may become pregnant should not use vanoprazon unless the anticipated therapeutic benefit is deemed to outweigh any potential risks. Patients who as mild, moderate, or severe hepatic abnormalities as well as participants with normal hepatic function were used to assess the impact of hepatic disorders on the pharmacokinetics of vonoprazan. The new potassium-competitive acid blocker (P-CAB) vonoprazan (TAK-438) was first approved worldwide in 2014 and became available for use as an acid suppressant in 2015. Recently, there have been reports of possible drug related(PK) interactions with vonoprazan. According to reports, CYP3A primarily drives the hepatic metabolism of vonoprazan through the cytochrome P450 pathway30.

Keywords: *Vanoprazan, Potassium-Competitive Acid Blocker (P-CAB), Proton Pump Inhibitors, Lasnoprazon, Pharmacokinectics (Pk), Pharmacodynamics.*

How to Cite: T. Rama Rao; D. Akshaya1; G. Sravya; T. Kaushik (2025) VONOPRAZAN: An Innovative Approach to Acid-Related Disorders. *International Journal of Innovative Science and Research Technology*, 10(2), 905-908. https://doi.org/10.5281/zenodo.14937088

I. INTRODUCTION

Among the most common conditions that affecting the upper gastrointestinal system is gastro-esophageal reflux disease (GERD), which causes stomach contents to reflux into the esophagus.Fewer symptoms include heartburn, dysphagia, belching, hiccups, nausea, and vomiting. Estimates indicate that 13.98% of adults globally have GERD, with prevalence varying from 4.16% in China to 22.40% in Turkey.

Acid-related conditions such as erosive esophagitis, gastric ulcer, duodenal ulcer, peptic ulcer, gastro-esophageal reflux, reflux esophagitis, and Helicobacter pylori eradication are being treated and prevented with vonoprazan, an oral bioavailable P-CAB.The P-CAB vonoprazan is being developed as an oral bioavailable medication to treat and prevent acid-related conditions such as erosive esophagitis, gastric ulcer, duodenal ulcer, peptic ulcer, gastro-esophageal reflux, reflux esophagitis, and Helicobacter pylori eradication.[2]

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14937088

Barrett's esophagus, erosive esophagitis, and non-erosive gastro-esophageal reflux disease are the three categories based on endoscopic signs.[3] For EE, acid suppression has been the standard treatment, and for the past few decades, proton pump inhibitors have been the preferred medication. Not withstanding the established effectiveness of acid-suppressing medications for both symptom relief and mucosal repair, some PPI-related drawbacks have recently been documented. The first is that many Numerous early PPI generations have a delayed onset of action, and it may take three to five days to reach maximal efficacy.[4]
*Dose include 10 mg and 20 mg.

II. SPECIAL PATIENT POPULATION

➢ *Impaired Renal Function*

This study evaluated the effect of renal disorders on vonoprazan PK in individuals with mild, moderate, or severe renal problems, end-stage renal disease (ESRD), and those with typical renal function. When patients who as mild, moderate, or intense renal disorders received a one vanoprazan dosage of (20 mg), their AUC and C were higher by 1.3 to 2.4 times and 1.2 to 1.8 times, respectively, than those with normal renal function. This suggests that vonoprazan exposure increases as renal function declines. In comparison to participants with typical renal function, ESRD patients had an AUC that was 1.3 times higher and a C_{max} that was 1.2 times higher**.**

➢ *Impaired Liver Function*

The impact of hepatic disorders on vonoprazan pharmacokinetics was assessed in individuals with mild, moderate, or severe hepatic problems as well as individuals with healthy liver function. When individuals with mild, moderate, or severe hepatic disorders received a single dosage of vonoprazan (20 mg), their AUC and C_{max}. were greater by 1.2 to 2.6 times and 1.2 to 18 times, respectively, than those with typical hepatic function.

➢ *Age, Gender, Race*

No research has done on vonoprazan in patients younger than eighteen. Vonoprazan has no clinically significant gender-related side effects.

➢ *Pregnancy*

To far, there have been no clinical studies evaluating vonoprazan in pregnant individuals. After being exposed to more than roughly 20 times the exposure (AUC) at the highest clinical dose (40 mg/day) of vonoprazan, embryo-foetal damage was noted in a toxicology study. Women who are or may become pregnant should not take vanoprazon as a precaution assuming that anticipated therapeutic benefit is deemed to outweigh any potential risks.

➢ *Lactation*

To present, no clinical trials have been carried out to assess vonoprazan in nursing participants. Although it has been demonstrated in animal experiments that vonoprazan is excreted in milk, it is unknown if this is the case in human milk.

III. MECHANISM OF ACTION

First approved globally in 2014, vonoprazan (TAK-438) is a new P-CAB that was introduced in 2015 for use as an acid suppressor. PPIs and P-CABs both affect the enzymehat bears responsibility for the crucial last stage of gastric acid secretion, gastric H+, K+-adenosine tri phosphatase (H+/K+-ATPase).[5]

Through irreversible covalent binding, PPIs inhibit by the activity of active phase H+/K+ ATPase; Its activation requires an acidic environment. Unlike PPIs, P-CABs use reversible K+-competitive ionic binding that is not dependent on stomach acid activation to inhibit the H+/K+ ATPase at both the active and resting stages. [6]

IV. PHARMACOKINETICS AND PHARMACODYNAMICS

Vonoprazan has a greater rate of medication compliance than PPIs because it is not impacted by food consumption and can be administred at any time in a day. Since vonoprazan is a weak and lipophilic base with a increased pKa value of 9.06 than PPIs (3.8–5.0), it is readily protonated and substantially accumulates in acidic spaces like parietal cells.[7]

➢ *Absorption*

Vonoprazan has time-independent PK, reaching steady state concentrations by Days 3–4. After seven days of multiple daily doses of vonoprazan, ranging from 10 to 40 mg (two times of the maximum recommended dose), administered to healthy volunteers, the drug's area under the plasma concentration time curve (AUC) and C values grew nearly dose proportionally. For doses between 10 and 40 mg (twice the maximum recommended dose), the accumulation index ratio based on AUC is less than 1.2, indicating minimum accumulation in plasma after once-daily repeated dosing. After taking 20 mg twice a day, the steady state plasma exposure of vonoprazan (AUC=273 hr ng/mL N=10) was around eight times greater than the mean estimate from the same participants on Day (AUC=155 hr ng/mL, N=10).

➢ *Distribution*

The mean binding rate of vonoprazan in human plasma (in vitro) is 85.2 to 88.0% when the concentration is between 0.1 and 10 pg/mL.

➢ *Metabolism*

The liver enzyme CYP3A4 is primarily accountable for the metabolism of, with CYP2B6, CYP2C19, and CYP2D6 also playing a role. Further, sulfotransferase SULT2A1 metabolizes vonoprazan. Time-dependent inhibition of CYP2B6, CYP2C19, and CYP3A4/5 is demonstrated by vonoprazan. Moreover, vanoprazon has a small inductive impact on CYP1A2 that is concentration-dependent, but it has no effect on CYP2B6 or CYP3A4/5.[8]

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14937088

➢ *Excretion*

When healthy adult male individuals are given a radioactively tagged medication (15 mg of vonoprazan) orally, 98.5% radioactivity will eliminated in urine and feces by 168 hours following management, 31.1% into feces and 67.4% into urine.

➢ *Contraindications*

- Individuals with a history of recognized hypersensitivity to vonoprazan or any of its constituents should avoid taking vonoprazan. Anaphylactic shock has been one of the reactions.
- Vonoprazan should not be used with products that contain rilpivirine.

➢ *Drug Interactions*

Recently, there have been reports of possible drug interactions with vonoprazan. Vonoprazan is reportedly processed mostly in the liver by CYP3A through the cytochrome P450 pathway30; hence, it is possible that vonoprazan interacts with other medications that are also being metabolized through this pathway. [9]

➢ *Example; Vanoprazan and Clarithromycin*

Vonoprazan (40 mg) was given as a single dose to healthy adult male volunteers 30 minutes after breakfast on days 1 and 8 with a recurrent dosage of 500 mg of potent clarithromycin twice a day, half an hour before breakfast and supper on days three through nine. In comparison to vonoprazan when given alone, the area under curve and C_{max} of vonoprazan rose by 1.6 and 14 times, correspondingly, when given concurrently with clarithromycin.

➢ *Vonoprazan and Low-Dose Aspirin or Vonoprazan and NSAIDs*

Vonoprazan 40 mg and aspirin 100 mg or NSAID (loxoprofen sodium 60 mg, diclofenac sodium 25 mg, or meloxicam 10 mg) concurrently did not appear to have any discernible effect on the pharmacokinetics of vonoprazan or low-dose aspirin or NSAIDs, according to a drug interaction study conducted in adult male individuals in good health.

➢ *Vanoprazon Compared with Lasnoprazon*

For patient who has previously history of stomach or duodenal ulcers who tested positive for H pylori, this phase III, randomised, double-blind, multicentre, parallel-group comparative research was conducted to confirm that vonoprazan is not inferior to lansoprazole as first-line triple therapy. Since lansoprazole accumulated in high concentrations and was gradually eliminated from the gastric gland, vonoprazan demonstrated more powerful and long-lasting acid-inhibitory effects in preclinical experiments, as well as larger rises in gastric pH. Vonoprazan single doses (1–120 mg) were well tolerated in healthy volunteers and had immediate, strong, and dose-related acid-inhibitory effects that persisted after multiple dosing (10–40 mg/day) over a period of seven days. Another phase II dose-ranging research found that over an 8-week period, vonoprazan (5–40 mg/day) achieved healing rates that were comparable to those of lansoprazole (30 mg/day) in participants with endoscopically confirmed erosive esophagitis. It was demonstrated that vonoprazan-based triple therapy was well tolerated and effective as first- and second-line therapies. Vonoprazan is a potentially effective novel treatment option that could be used in conjunction with other therapeutic techniques, such as sequential, quadruple, and long-term therapy for the elimination of H pylori.[10]

➢ *Vanoprazon Compared With Other PPIs*

- Forty-two studies out of the 4001 papers found in the database qualified. After a manual search, one study was included in the analysis. The odds ratios (ORs) for vonoprazan (20 mg daily) compared to esomeprazole (20 mg), rabeprazole (20 mg), lansoprazole (30 mg), and omeprazole (20 mg) were 2.29 (95% CI 0.79–7.06), 3.94 (1.15–14.03), 2.40 (0.90–6.77), and 2.71 (0.98–7.90) for the primary examination of healing effects at 8 weeks. In the subgroup analysis for patients with severe esophagitis at baseline, vonoprazan's ORs were significantly higher than those of other comparator PPIs.According to this investigation, vonoprazan has a stronger GERD-healing effect than rabeprazole (20 mg), but not more so than other PPIs. According to subgroup analysis, vonoprazan works better for individuals with severe erosive esophagitis than the majority of PPIs.[11]

- PPIs and vonoprazan 20 mg randomized controlled trials published in English were searched. Two researchers extracted data from studies that met the eligibility requirements separately, and they compared the results to ensure consistency. Our results imply that vonoprazan is not less effective than PPIs as a GERD treatment. For patients with severe erosive esophagitis, vonoprazan is more efficacious than PPIs, according to subgroup analysis. Compared to PPIs, vonoprazan has comparable safety results. After searching the databases for fifty-six articles, one study was manually located and included in the analysis, providing a total of six relevant studies. Efficacy and adverse event risk ratios (RR) for vonoprazan and PPIs were 1.06 (0.99–1.13) and 1.08 (0.96–1.22), respectively, for the primary analysis. Vonoprazan had a substantially higher RR of 1.14 (1.06–1.22) than lansoprazole in the subgroup study of patients with baseline severe esophagitis.[12]

V. DISCUSSION

Vonoprazan offers a promising new option for the treatment of acid-related gastrointestinal disorders, including GERD. Its rapid and sustained acid suppression, higher efficacy in severe GERD cases, and favorable pharmacokinetic profile make it a valuable alternative to traditional PPIs. While it demonstrates potential in both standard GERD treatment and H. pylori eradication regimens, careful consideration of its use in patients with renal or hepatic impairment, as well as pregnant or lactating women, is essential. Ongoing research and clinical trials will provide further insights into its role in the broader management of GERD and other acid-related conditions.

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14937088

VI. CONCLUSIONS

Vonoprazan, is a new potassium competitive acid blocker with distinct pharmacological and pharmacokinetic characteristics, has a number of advantages over proton pump inhibitors, including a quicker onset of action and more powerful and long-lasting acid suppression. Current clinical trials have demonstrated that vonoprazan is not clinically inferior to traditional PPIs for the treatment of EE. Consequently, vonoprazan may be a new option for the treatment of EE, particularly for patients with greater grades of erosive esophagitis and those who are resistant to PPIs. Notably, the choice of PPIs and their administration method may affect the outcomes. Several studies contrasting PPIs and vonoprazan.

Future research should examine the effectiveness of vonoprazan in treating erosive esophagitis when combined with a PPI at standard or higher dosages given once or twice daily. Vonoprazan is currently undergoing clinical trials for the treatment of erosive esophagitis in non-Asian populations, and these are promising. Crucially, as vonoprazan's indications continue to grow, its extended safety profile needs to be carefully examined. Future research is necessary to examine the cost-effectiveness and optimal strategies of vonoprazan-based therapy, including the best dosage, duration of treatment, cessation, etc.

REFERENCES

[1]. Sadafi, S., Azizi, A., Pasdar, Y. et al. Risk factors for gastroesophageal reflux disease: a population-based study. BMC Gastroenterol 24, 64 (2024). https://doi.org/10.1186/s12876-024-03143-9).

[2]. Garnock-Jones KP. Vonoprazan: first global approval. Drugs. 2015 Mar;75(4):439-43. doi: 10.1007/s40265-015-0368-z. PMID: 25744862.

[3]. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut. 2018 Mar;67(3):430-440. doi: 10.1136/gutjnl-2016-313589. Epub 2017 Feb 23. PMID: 28232473.

[4]. Tytgat GN. Shortcomings of the first-generation proton pump inhibitors. Eur J Gastroenterol Hepatol. 2001 May;13 Suppl 1:S29-33. PMID: 11430506.

[5]. Shin JM, Munson K, Vagin O, Sachs G. The gastric HK-ATPase: structure, function, and inhibition. Pflugers Arch. 2009 Jan;457(3):609-22. doi: 10.1007/s00424-008-0495-4. Epub 2008 Jun 6. Erratum in: Pflugers Arch. 2011 Mar;461(3):399. PMID: 18536934; PMCID: PMC3079481.

[6]. Shin JM, Sachs G. Long lasting inhibitors of the gastric H,K-ATPase. Expert Rev Clin Pharmacol. 2009 Sep;2(5):461-468. doi: 10.1586/ecp.09.33. PMID: 21132072; PMCID: PMC2995460.

[7]. Shin JM, Inatomi N, Munson K, Strugatsky D, Tokhtaeva E, Vagin O, Sachs G. Characterization of a novel potassium-competitive acid blocker of the gastric H,K-ATPase, 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438). J Pharmacol Exp Ther. 2011 Nov;339(2):412-20. doi: 10.1124/jpet.111.185314. Epub 2011 Aug 9. PMID: 21828261; PMCID: PMC3199995.

[8]. Munson K, Law RJ, Sachs G. Analysis of the gastric H,K ATPase for ion pathways and inhibitor binding sites. Biochemistry. 2007 May 8;46(18):5398-417. doi: 10.1021/bi062305h. Epub 2007 Apr 11. PMID: 17425287; PMCID: PMC2837483.

[9]. Wang Y, Wang C, Wang S, Zhou Q, Dai D, Shi J, Xu X, Luo Q. Cytochrome P450-Based Drug-Drug Interactions of Vonoprazan *In Vitro* and *In Vivo*. Front Pharmacol. 2020 Feb 14;11:53. doi: 10.3389/fphar.2020.00053. PMID: 32116727; PMCID: PMC7033572.

[10]. Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study. Gut. 2016 Sep;65(9):1439-46. Doi: 10.1136/gutjnl-2015-311304. Epub 2016 Mar 2. PMID: 26935876; PMCID: PMC5036253.

[11]. Miyazaki H, Igarashi A, Takeuchi T, Teng L, Uda A, Deguchi H, Higuchi K, Tango T. Vonoprazan versus proton-pump inhibitors for healing gastroesophageal reflux disease: A systematic review. J Gastroenterol Hepatol. 2019 Aug;34(8):1316-1328. Doi: 10.1111/jgh.14664.

[12]. Cheng, Y., Liu, J., Tan, X. et al. Direct Comparison of the Efficacy and Safety of Vonoprazan Versus Proton-Pump Inhibitors for Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis. Dig Dis Sci 66, 19–28 (2021). https://doi.org/10.1007/s10620-020-06141-5)