ORIGINAL ARTICLE

EFFICACY AND COST-EFFECTIVENESS, COMPARISON OF 7-DAYS VONOPRAZAN VERSUS 14-DAYS ESOMEPRAZOLE BASED TRIPLE THERAPIES FOR TREATING *HELICOBACTER PYLORI* INFECTION IN PAKISTANI POPULATION: A RANDOMIZED CLINICAL TRIAL

Farzana Waqar[1], Mudassar Noor[1], Kulsoom Farhat[1], Shabana Ali[1], Ehtesham Haider[2], Syedah Fauzia Fatima Gillani[1]

[1]Department of Pharmacology, Army Medical College, National University of Medical Sciences, Rawalpindi-Pakistan
[2]Department of Gastroenterology, Pak Emirates Military Hospital, Rawalpindi-Pakistan

Background: Helicobacter pylori (*H. pylori*) is a gram-negative bacterium which usually resides in the mucoid lining of the stomach and may cause different gastric pathologies e.g., Gastritis, peptic ulcer disease, adenocarcinoma of the gastric system and mucoid associated lymphoma (MALT). The Objective was to compare the effect of 7-days Vonoprazan based triple therapy and 14-days Esomeprazole based triple therapy on eradication rate, compliance and cost effectiveness in *Helicobacter pylori* infected patients. **Methods:** This clinical trial was performed in the Department of Pharmacology Army Medical College, National University of Medical Sciences (NUMS) in collaboration with the Gastroenterology Department, Pak Emirates Military Hospital (PEMH) Rawalpindi from December 2022 to March 2023. A total of one hundred and twenty-two patients with dyspepsia symptoms and yielding lab results positive for Helicobacter pylori by stool antigen test were enrolled in the study. They were randomly allocated into two groups. The Esomeprazole group received 14 days of triple therapy orally with Esomeprazole 20 mg twice a day; Amoxicillin 1000 mg twice a day; and Levofloxacin 500 mg one time a day. The comparative Vonoprazan group was given 7-days triple therapy orally with Vonoprazan 20 mg twice a day; Amoxicillin 1000 mg twice a day; and Levofloxacin 500 mg one time a day. Eradication success was evaluated by stool antigen test four weeks later, as counted from the start of treatment. compliance and cost-effectiveness of both therapies were also assessed. **Results:** The eradication rate was (95.1%) in the Vonoprazan group with 58 out of 61 patients negative for *H. pylori* and (93.1%) in Esomeprazole group with 54 patients out of 58 yielding a negative result demonstrating *p*-value of 0.64. Compliance was 95.0% in the Esomeprazole group with *p*-value of 0.07. Cost effective ratio for Vonoprazan triple therapy was lower (731.8PKR) than the Esomeprazole group. **Conclusion:** One two-week Vonoprazan regimen demonstrated improved eradication rate, good compliance, and better tolerability in patients with less cost and a half duration of treatment in comparison with two weeks Esomeprazole regimen, attesting that one week Vonoprazan therapy is more cost efficacious in producing better results.

Keywords: Helicobacter pylori; Eradication; Cost effectiveness; Vonoprazan; Esomeprazole

Citation: Waqar F, Noor M, Farhat K, Ali S, Haider E, Gillani SFF. Efficacy and Cost-effectiveness, Comparison of 7-Days Vonoprazan versus 14-Days Esomeprazole based Triple Therapies for Treating Helicobacter Pylori Infection in Pakistani Population: A randomized clinical trial. J Ayub Med Coll Abbottabad 2023;35(4 Suppl 1):746–51.

DOI: 10.55519/JAMC-S4-12110

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium which usually resides in the mucoid lining of the stomach and may cause different gastric pathologies e.g., Gastritis, peptic ulcer disease, adenocarcinoma of the gastric system and mucoid associated lymphoma (MALT). It affected around 50% of the world's population since its first confirmed human isolation in 1982 by Warren and Marshal.[1,4] Its prevalence varies between 10–90% worldwide. *H. pylori* is the most frequently occurring infection in developing countries like Pakistan, where the population get infected at an early age in comparison with the western region. Low socioeconomic status and poor hygiene are the contributory factors in our country.[2]

A change in the gastric pH by acid-inhibitory drugs further increases the stability and bioavailability of acid-sensitive antimicrobial agents, making them more effective against *H. pylori*.[3] An early and complete eradication therapy of *H. pylori* can prevent disease progression and resultantly inhibit advancement to Gastric Carcinoma and mortality. As acid inhibition not only relieves *H. pylori* related symptoms but can also augment anti-biotics effect due to less exposure time of the drug in an acid concentrated gastric environment.[5] The management of *H. pylori* infection guidelines in Pakistan also recommend the use of traditional first- and second-line

agents inclusive of Clarithromycin triple therapy, Proton pump inhibitor (PPI), Clarithromycin, Amoxicillin/Metronidazole, Quadruple containing Bismuth and sequential therapies.[6] Global literature in the last decade reported lower *H. pylori* eradication rates (<80%) with clarithromycin resistance in European countries and Asia.[6]

PPI-based *H. pylori* elimination treatment regimens haven't been effective in antibiotic resistant populations, and there was insufficient evidence to support the effectiveness of increasing the dosage of traditional agents. Resistance to antibiotics remains a problem in the population of Pakistan and the main factor that contributed to the failure of triple therapy for *H. pylori* is clarithromycin resistance. Vonoprazan a novel acid inhibiting drug first experimented with in 2015 for acid inhibition in other gastric conditions and also a part of eradication therapy for *H. pylori*, considered 350 times more potent than PPI for acid inhibition through reversible potassium ion inhibition to H+ K+ ATPase pump in the process of acid synthesis in the parietal cells of the stomach. Vonoprazan based triple, dual and quadruple therapies are proving very beneficial in controlling this notorious infection.[7] Current treatment guiding principle for *H-pylori* eradication recommended Vonoprazan based triple therapy for one week duration as an alternative to PPI for rapid eradication rate, patient symptoms and life quality improvement and cost effectiveness in developing countries like Pakistan due to poor socioeconomic conditions. As we analyze from a global perspective, healthcare costs have been rising for several decades, and the reasons for this are complex. There are several factors contributing to the increase in healthcare costs, including, new medical technologies, such as diagnostic tests, imaging procedures, and varying treatment modalities that are continuously being developed. A peeking look at our national health economics from this perspective, Pakistan being a developing nation has had a considerable increase in healthcare spending in the last decade, with a most rapid spike in the last three years after the Pandemic. Keeping in view this fact, this necessitates an approach for determining the cost effectiveness of any medical management plan encompassing prolonged treatment. This shall determine the justification for prescribing the drug in terms of treatment success rate while assuring affordability for the target population seeking the required treatment.[4]

The highly prevalent *H. pylori* infection in Pakistan also upscales the economic burden on the health care system with an increasing cost of the medicines required to eradicate this gram negative bacterium. Therefore, short duration treatment with a more potent acid inhibiting drug, seven-day Vonoprazan based triple therapy is the foremost inevitability for the notorious infection with less cost.

MATERIAL AND METHODS

This open labelled clinical study was conducted from December 2022 to March 2023 in the Department of Pharmacology Army Medical college, NUMS in collaboration with the Gastroenterology Department, Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan. Ethical approval was taken from the respective ethical review committees of both institutes. A sample size of 122 was calculated by using the reported prevalence of *H. pylori* infection and keeping the confidence interval 95%, and 7% absolute precision, through the WHO calculator. The participants included in the study were all those aged above 18 years of both genders with dyspepsia symptoms, positive for *H. pylori* by stool antigen test. The exclusion criteria were allergy to the medicines used in triple therapies, history of previous *H. pylori* eradication therapy, pregnancy, lactation, history of serious cardiovascular, renal, or liver disease, gastric malignancy or surgery and a history of drug addiction.

An informed consent was taken followed by a random allocation of the patients who fulfilled the inclusion criteria. This was carried out by computer generated blocks and they were kept in either the Esomeprazole group (n=61) with two weeks of Esomeprazole based triple therapy or the Vonoprazan group (n=61) with one week of Vonoprazan based triple therapy in a 1:1parallel manner. The sample technique was nonprobability purposive sampling. The medicines in the Esomeprazole group were Esomeprazole 20mg twice a day; Amoxicillin 1000 mg twice a day; and Levofloxacin 500 mg one time a day for 14-days, whereas in the Vonoprazan group were Vonoprazan 20 mg twice a day; cap Amoxicillin 1000 mg twice a day; Levofloxacin 500mg one time a day for 7-days. After they were allocated in the subsequent groups, their demographic and socioeconomic details were noted. Good compliance and better tolerability of the prescribed medication are essential requirements for the success of that treatment regimen. For assessment of the compliance, they were called for follow-up visit to the Hospital after one week of the commencement of the triple therapy medication. Patients who took less than 90% of the medication and left the therapy before completing the required treatment duration, were considered non-compliant.

Patients of both groups were counselled on the importance of follow-up visits for the confirmation of *H. pylori* eradication test at week 4 after starting the eradication therapy. At the post treatment follow up, the stool antigen test for *H. pylori* was done for confirmation of treatment success. Effectiveness of the

therapies was calculated from outcome percentages. The cost effectiveness of both treatment regimens was also analysed, first of all, the individual cost for each drug was calculated and then the total cost, which was the direct medical cost per person and then the total cost per 61 patients in both regimens was calculated. In the end cost effectiveness ratios were calculated by dividing the total cost per 61 patients of each therapy by the total outcome of each treatment regimen.8 The data was analysed by using IBM-SPSS statistics version 27, wherein for categoric data, Frequencies and percentages were computed, whilst, for quantitative variables, Mean and ±SD were calculated. The chi-square test was used to assess the significance level of the data. *p*-value of <0.05 was considered significant. Figure-1 shows the consort diagram for randomization and allocation of patients into subsequent group

RESULTS

One hundred and thirty-five patients were evaluated for eligibility criteria of the study, out of which thirteen were excluded. One hundred and twenty-two were randomized, sixty-one in each group, three patients in the Esomeprazole group did not adhere to the medicine and lost their follow up visit. One hundred and twenty-two (122) patients were analysed for baseline data and one hundred and nineteen were assessed for study parameters. The study enrolment had a gender distribution of 65(53.2%) males and 57(46.72%) females. In the Esomeprazole group, there were 30 males (49.1%) and 31 females (50.8%) while in the Vonoprazan group, there were 35 (57.37%) males and 26(42.62%) females.

The *p*-value of gender distribution in both the groups,0.36 is insignificant. Mean age ±SD in Esomeprazole group was 38.40±12.25 and in Vonoprazan group it was 40.98±12.13, which is statistically insignificant with *p*-value of 0.07. In Esomeprazole group, out of 58 patients 54 were *H. pylori* negative and 4 were positive with an eradication rate of 93.1% at week 04 after starting the eradication therapy. In Vonoprazan group with one week therapy, out of 61 patients 58 were negative while 3 were positive for *H. pylori* with an eradication rate of 95.1%, demonstrated better eradication rate in spite of one week difference of duration of therapy, thus proving the high efficacy of Vonoprazan in comparison with Esomeprazole. Eradication rates details are given in the Figure 2.

Compliance of both the therapies was also analysed, 3 out of 61 patients were non-compliant to Esomeprazole based triple regimen, so compliance was 95.0% in Esomeprazole group in comparison with 100% compliance in Vonoprazan triple regimen predicted *p*-value of 0.07. This proved efficacy of one-week Vonoprazan based triple regimen.

At last, the cost effectiveness of both the triple treatments was calculated. Cost per patient in Vonoprazan group was 1141PKR in comparison with 1782PKR of Esomeprazole regimen. Cost effectiveness ratio of Vonoprazan group was (731.8PKR) lower than Esomeprazole based regimen. Details of cost of all the drugs in both the triple therapy regimen, manufactured by Getz® Pharmaceutical company Pakistan and total cost of each regimen is presented in table 1and cost effectiveness ratio details are given in table 2.

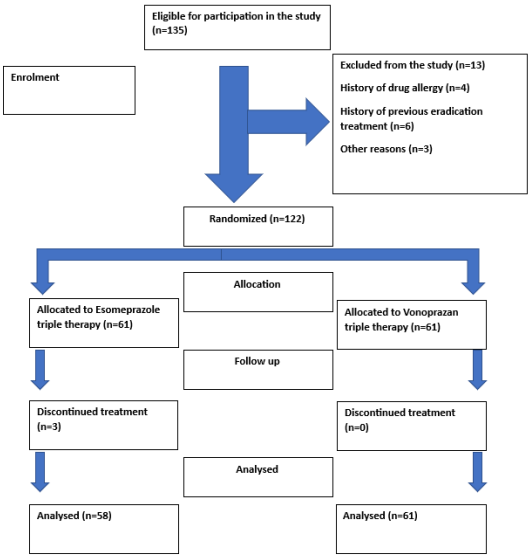

Figure-1: Randomization and allocation of the patient in the consort diagram

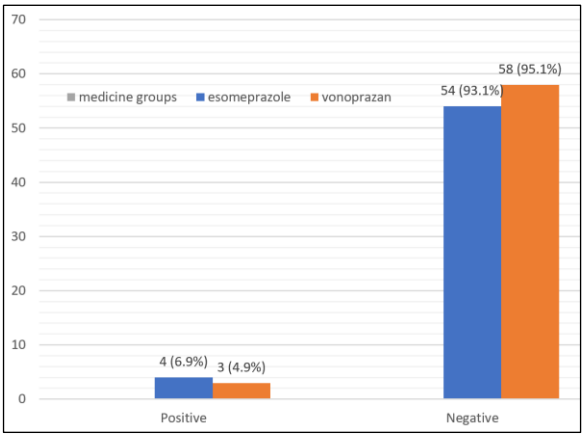

Figure 2. Graphical representation of positive and negative percentages after completion of the treatment

Table-1: Treatment regimens and detailed cost of both therapies

Treatment Regimens	Dose per day (mg)	Duration of therapy (days)	Cost per tablet (PKR)	Cost per drug (PKR)	Total cost of each drug (PKR)	Total cost of therapy (PKR)
14 -days Esomeprazole triple therapy						
Esomeprazole (NEXUM)®	2X20	14	21	42	592	1782
Levofloxacin (LEFLOX)®	1x500	14	41	41	574	
Amoxicillin (OSPAMOX)®	2x1000	14	22	44	616	
7-days Vonoprazan triple therapy						
Vonoprazan (VONOZAN)®	2x20	7	39	78	546	1141
Levofloxacin (LEFLOX)®	1x500	7	41	41	287	
Amoxicillin (OSPAMOX)®	2x1000	7	22	44	308	

Table-2: Calculation of cost-effectiveness Ratios for both the treatment groups

Treatment Regimens	The overall cost of 61 patients (PKR)	Outcome %	Cost-effectiveness ratio (CER) = (total cost/outcome) (PKR)
Esomeprazole triple therapy	108,702	93.1	1167.5 PKR
Vonoprazan triple therapy	69,601	95.1	731.8 PKR

DISCUSSION

It is recommended to treat *H. pylori* infection to minimize the risk of more serious complications and to avoid the associated costs of diagnosis and treatment. Previously PPIs PPIs-based triple, Quadruple and sequential therapies were considered as a first choice for eradicating *H. pylori*. Multiple reasons for the failure of these regimen now lead to replace conventional PPI based regimen with Vonoprazan a more potent acid inhibiting drug based therapies. Current study with 7-days Vonoprazan based triple therapy demonstrated 95.1% eradication rate in comparison with 93.1% of Esomeprazole based triple therapy, proved the effectiveness of this short duration therapy not only in eradicating bacteria quickly but also produced 100% compliance, better tolerability and a lower cost effectiveness ratio of 731.8 PKR in *H. pylori* infected patients.

Better eradication rate was the first outcome of the present study, Likewise, Suzuki and his companions also performed a randomized multi centered clinical trial for one week of medication of Vonoprazan with low-dose,750mg Amoxicillin double therapy as the initial line therapies for control of *H. pylori* infection. The Vonoprazan double and Vonoprazan triple treatments had eradication percentages of 84.5% & 89.2%, respectively in this trial. Vonoprazan double exhibited significantly higher eradication rates for isolates that were resistant to Clarithromycin in comparison to Vonoprazan triple therapy. The one-week Vonoprazan triple therapy and low-dose Amoxicillin double treatment generated satisfactory *H. pylori* eradication proportions and a similar result to Vonoprazan-centered combination therapy in areas with significant levels of Clarithromycin resistance. The eradication percentages in the above one week trial are not coinciding with the current study results. They used low doses of antibiotics with Vonoprazan both in double and triple regimens in comparison with our trial, we also replaced Clarithromycin with single dose Levofloxacin and thus reduced the chance of eradication failure due to Clarithromycin. This is the explanation for lower outcomes than the current one week Vonoprazan based study.[9] Similar to the above study another effort put by Maruyama *et al.* who organized a prospective study to calculate the effectiveness of Vonoprazan as an initial therapy choice in comparison to the PPI for one week duration. The eradication rate was significantly higher in Vonoprazan centered therapy group (95.8%) in comparison to PPI group (69.6%). The Vonoprazan centered therapy was proved more effective than PPI centered therapy as the initial choice for the *H. pylori* eradication. Result of Vonoprazan based treatment in the above study support our trial findings, although we used different antibiotics combination but doses of acid inhibiting drugs and duration of treatment were the same in both the studies.[10]

Another important finding in our study was 100% compliance with *p*-value of 0.07 in 7-days Vonoprazan based triple therapy. Different clinical studies performed worldwide have made comparison of Vonoprazan based therapies with Omeprazole based therapies not only for the efficacy and safety assessment but they also noted compliance of the participants in both the treatment groups. A recent meta-analysis of eight clinical trials with first line

triple therapies of both acid inhibiting drugs based performed by a group of researchers in 2023, comprises of sun and his fellows also documented that Vonoprazan based regimens were more tolerable and they had better compliance in comparison with Omeprazole based treatment like current one week Vonoprazan therapy. Compliance of the patients in those clinical trials included in the above meta-analysis was assessed by dropout of the patient from the study after starting the eradication treatment. The majority of the patient were compliant and well tolerated the medicines in Vonoprazan group in comparison with Omeprazole based regimen. These results provide support to the current study results regarding tolerability and compliance of the patients in one week Vonoprazan based regimen.[11]

We also analysed the pharmacoeconomic cost effectiveness of both the treatment regimens, as the cost is an important contributing factor in the success of any treatment modality especially in a country with poor socioeconomic background like Pakistan. The added beneficiary effect of the current novel one week Vonoprazan based regimen in our low socioeconomic status is its cost effectivity. One week Vonoprazan based therapy had low cost of therapy as the doses of antibiotics were reduced to fifty percent of its usage in Esomeprazole triple therapy for two weeks. Vonoprazan therapy costs 1141 PKR while Esomeprazole treatment costs 1782 PKR. One week Vonoprazan produced the lowest cost effective ratio of 731.8 PKR in comparison with 1167.5 PKR of two weeks Esomeprazole based treatment. This is a positive contributing factor for the implementation of this one week Vonoprazan regimen for highly prevalent *H. pylori* eradication in our country. Kajihara and his colleagues 2017 in a retrospective analysis of 209 patients of *H. pylori* infection, also determined the cost effectiveness ratio of both Vonoprazan and Omeprazole triple therapies. The cost effectiveness ratio for Vonoprazan based regimen was 360.1 JPY in comparison with 379.4 JPY for PPI based treatment. The result of cost effectiveness of this retrospective study is in alliance with current prospective study. the above study had large sample size and prolong duration of data collection than the current Vonoprazan based regimen.[12] In a literature review performed by M. Shehryar and his colleagues, about the cost effectiveness of Vonoprazan and PPI based therapies in *H. pylori* infection, they made comparison of the cost of both Rabeprazole based and Vonoprazan based regimens not only for *H. pylori* eradication treatment but also for reflux esophagitis. As this meta-analysis included studies conducted in Japan, So the cost-effective ratio of PPI was 58 JPY/day while for Vonoprazan based treatment it was 68 JPY /day in reflux esophagitis directed that Vonoprazan regimens were cost effective in both eradicating *H. pylori* and other GIT disorders. These results coincide with the current one week study result on cost effectiveness of the therapy.[13] This short duration therapy for *H. pylori* infection could have both clinical and economic benefits in Pakistan. Which can improve compliance and tolerability, making it easier for patients to complete their treatment and achieve a cure. Additionally, reducing the duration of treatment can help to lower the economic burden on patients, especially those from low socioeconomic backgrounds. *H. pylori* infection is a significant public health concern in Pakistan, with a high prevalence in the population. By implementing short duration therapy, healthcare providers can help to reduce the burden of this infection and improve health outcomes for patients. It's essential to continue developing and implementing effective treatment modalities to address the unique healthcare challenges faced by the population in Pakistan. The limitation of study was small sample size and single centre for data gathering, multicentred study with an increased sample size is suggested to further strengthen our hypothesis.

CONCLUSION

The eradication rate and compliance of the patient improved with 7-days of Vonoprazan based therapy with less treatment cost. It would be a better option for clinicians for the treatment of highly prevalent *H. pylori* infection.

Conflict of interest: I have no conflict of interest to disclose in my study.

AUTHORS' CONTRIBUTION

FW: Principal Researcher and author. MN: Academic Supervisor and Questionnaire Design. KF: Study design and approval. SA: Literature search. EH: Clinical supervisor and data collection. SFFG: Data analysis and drafting

REFERENCES

1. Zamani M, Ebrahimtabar F, Zamani V, Miller W, Alizadeh-Navaei R, Shokri-Shirvani J, *et al*. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther 2018;47(7):868–76.
2. Gunaratne AW, Hamblin H, Clancy A, Magat AJMC, Dawson MVM, Tu J, *et al*. Combinations of antibiotics and vonoprazan for the treatment of Helicobacter pylori infections—Exploratory study. Helicobacter 2021;26(5):e12830.
3. Argueta EA, Moss SF. How we approach difficult to eradicate Helicobacter pylori. Gastroenterology 2022;162(1):32–7.
4. Pourfarzi F, Moghadam TZ, Zandian H, Malekzadeh R, Yazdanbod A. Cost-effectiveness analysis of two routine therapeutic methods for Helicobacter pylori eradication: a Persian cohort-based study. Gastroenterol Hepatol Bed Bench 2021;14(3):250–9.
5. Aishwarya M, Kannan I, Sucharitha ST. In silico design of primers and development of PCR-RFLP test for the detection of antibiotic sensitivity in Helicobacter pylori. Glob J Innov Med Sci 2022;1(1):38–44.

6. Kamani L, Ahsan M, Butt N, Luxmi S, Khan JUA, Khan E, *et al*. Helicobacter Pylori Management Guidelines from Pakistan. J Pak Med Assoc 2022;72(7 Suppl 2):4–11.
7. Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW. Vonoprazan triple and dual therapy for Helicobacter pylori infection in the United States and Europe: Randomized clinical trial. Gastroenterology 2022;163(3):608–19.
8. Farhoud NS, Ibrahim OM, Ezzat SE. Efficacy and cost-effectiveness comparison of 10-day, 14-day sequential versus 14-day triple therapies for treating Helicobacter pylori infection in Egyptian patients. J Clin Gastroenterol 2020;54(9):806–12.
9. Suzuki S, Gotoda T, Kusano C, Ikehara H, Ichijima R, Ohyauchi M, *et al*. Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line Helicobacter pylori treatment: a multicentre randomised trial in Japan. Gut 2020;69(6):1019–26.
10. Maruyama M, Tanaka N, Kubota D, Miyajima M, Kimura T, Tokutake K, *et al*. Vonoprazan-based regimen is more useful than PPI-based one as a first-line Helicobacter pylori eradication: a randomized controlled trial. Can J Gastroenterol Hepatol 2017;2017:4385161.
11. Sun Y, Yue L, Hu W. Effectiveness and safety of vonoprazan-based regimens compared with those of proton pump inhibitor (PPI)–based regimens as first-line agents for Helicobacter pylori: a meta-analysis of randomized clinical trials. Eur J Clin Pharmacol 2023;79(2):279–88.
12. Kajihara Y, Shimoyama T, Mizuki I. Analysis of the cost-effectiveness of using vonoprazan–amoxicillin–clarithromycin triple therapy for first-line Helicobacter pylori eradication. Scand J Gastroenterol 2017;52(2):238–41.
13. Shehryar M, Ahmad RU, Kareem HK, Khan L, Ashraf MF, Hassan A, *et al*. Efficacy, safety and cost-effectiveness of vonoprazan vs Proton Pump Inhibitors in reflux disorders and *H. pylori* eradication: A literature review. Ann Med Surg 2022;82:104760.

Submitted: May 28, 2023	*Revised: January 1, 2024*	*Accepted: January 11, 2024*

Address for Correspondence:

Farzana Waqar, Department of Pharmacology, Army Medical College, National University of Medical Sciences, Rawalpindi-Pakistan
Email: drfaru11@gmail.com