Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: http://www.tandfonline.com/loi/ieop20

Vonoprazan Fumarate for the Management of Acid-Related Diseases

Irene Martinucci, Corrado Blandizzi, Giorgia Bodini, Elisa Marabotto, Vincenzo Savarino, Santino Marchi, Nicola de Bortoli & Edoardo Savarino

To cite this article: Irene Martinucci, Corrado Blandizzi, Giorgia Bodini, Elisa Marabotto, Vincenzo Savarino, Santino Marchi, Nicola de Bortoli & Edoardo Savarino (2017): Vonoprazan Fumarate for the Management of Acid-Related Diseases, Expert Opinion on Pharmacotherapy, DOI: 10.1080/14656566.2017.1346087

To link to this article: http://dx.doi.org/10.1080/14656566.2017.1346087

Accepted author version posted online: 28 Jun 2017.

Publisher: Taylor & Francis

Journal: *Expert Opinion on Pharmacotherapy*

DOI: 10.1080/14656566.2017.1346087

Vonoprazan Fumarate for the Management of Acid-Related Diseases

Irene Martinucci MD[1], Corrado Blandizzi MD[2], Giorgia Bodini MD[3], Elisa Marabotto MD[3], Vincenzo Savarino MD[3], Santino Marchi MD[1], Nicola de Bortoli MD[1], Edoardo Savarino MD, PhD[1]

[1] Division of Gastroenterology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

[2] Division of Pharmacology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[3] Division of Gastroenterology, Department of Internal Medicine, University of Genoa, Genoa, Italy

[4] Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

Corresponding author:

Edoardo Savarino, MD

Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

Via Giustiniani 2

35128 - Padova - Italy

Phone: +39 0498217749

Fax: +39 0103538956

E-mail: edoardo.savarino@unipd.it

Funding
This paper was not funded

Declaration of Interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Authors contributions:
Irene Martinucci, Corrado Blandizzi and Edoardo Savarino have contributed to the design of the study, data collection, writing of the manuscript, and approval of the final manuscript.
Giorgia Bodini, Elisa Marabotto, Vincenzo Savarino, Santino Marchi, Nicola de Bortoli have contributed to the design of the study, data collection and approval of the final manuscript.

ABSTRACT

Introduction: Proton pump inhibitors (PPIs) display a number of limitations and unmet clinical needs that have prompted the development of novel drugs to improve the outcomes of acid-related diseases, including the eradication of H. pylori. In this context, a new synthesized potassium-competitive acid blocker (P-CAB), vonoprazan, showed higher suppression of gastric acid secretion.

Areas covered: This review discusses the current knowledge regarding the efficacy of vonoprazan in the treatment of acid-related diseases, with a particular focus on its use in Helicobacter pylori eradication.

Expert opinion: Vonoprazan showed some advantages over PPIs in terms of the pharmacokinetic and pharmacodynamic profile: fast onset of action without requiring acid activation and specific administration timing, more potent and prolonged inhibition of acid secretion, including a better nighttime acid control, and a less antisecretory variability. Recent evidence suggests that vonoprazan can be preferred to PPIs as maintenance therapy for reflux esophagitis and eradication of Helicobacter pylori owing to its stronger antisecretory effect. Moreover, vonoprazan displays favorable safety and tolerability profiles, even though long-term studies on the effects of vonoprazan are required.

Key Words: Vonoprazan, Gastro-esophageal Reflux Disease, GERD, Pharmacokinetics, P-CABs

1. Introduction

The identification of proton pump (H^+,K^+-ATPase) as the final step of gastric acid secretion and the subsequent development of its blockers (proton pump inhibitors, PPIs) have led to a dramatic improvement in the therapeutic management of acid-related digestive disorders and their complications, thus minimizing the role of surgery.[1] Currently, PPIs represent one of the most commonly prescribed class of drugs both in gastroenterology and primary care, and are regarded as the treatment of choice for acid-related diseases, including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), upper gastrointestinal (GI) adverse events associated with non-steroidal anti-inflammatory drugs (NSAIDs), and *Helicobacter pylori* (*H. pylori*) infection in combination with antibiotics.[1, 2] Despite their proven efficacy for the induction and maintenance of symptom relief, mucosal healing, as well as prevention of recurrence and complications,[3, 4] the management of acid-related disorders remains subject to a number of challenges that can be attributed, at least in part, to shortcomings and limitations pertaining to PPIs, as briefly summarized in Table 1. [5, 6] In particular, failure or incomplete response to these drugs has been reported from 10 to 40% of GERD patients.[7] Furthermore, several lines of evidence are pointing out an increasing prevalence of antibiotic resistance and decrease in eradication rates of *H. pylori* infection associated with treatment regimens that include PPIs.[8, 9] Recently, we have reviewed and discussed in detail the main determinants underlying the antisecretory effect and limitations of PPIs, to which we refer for an in-depth analysis.[10]

The above considerations have fostered the research towards the development of new acid suppressive agents, in an attempt of overcoming PPI limitations.[6, 11] In this context, the most promising strategies have included: 1) new formulations of current PPIs; 2) new PPIs (i.e., tenatoprazole, ilaprazole); 3) new proton pump blockers endowed with alternative mechanisms of action than irreversible PPIs (i.e., potassium-competitive acid blockers, P-

CABs).[12-14] Within the latter line, a novel P-CAB, vonoprazan, designated also as vonoprazan fumarate or TAK-438, has been developed and approved for clinical use in Japan since February 2015.[15, 16] As vonoprazan has a long duration of action and causes rapid and strong inhibition of gastric acid secretion, it has gained clinical attention for treatment of acid-related diseases.[16]

In the present review, we discuss the current knowledge regarding the efficacy of vonoprazan in the treatment of acid-related diseases, with a particular focus on its use in *H. pylori* eradication, which has been matter of investigation in several recent trials.

2. P-CABs

P-CABs comprise a heterogeneous class of compounds able to inhibit selectively the gastric H^+,K^+-ATPase by a specific, reversible mechanism of competition for the K^+ site.[17, 18] When compared to irreversible PPIs, the pharmacological profiles of P-CABs display peculiarities that justify great expectations and benefits from a clinical standpoint. In particular, P-CABs are lipophilic, weak bases endowed with a higher pKa than PPIs. Owing to these features, following their absorption into the systemic circulation P-CABs are highly concentrated within the secretory canalicula of parietal cells, where they are exposed to a highly acidic environment and instantly protonated. Immediately thereafter, P-CABs are thought to bind the K^+ site on H^+,K^+-ATPase and inhibit the proton pump function by a competitive displacement of K^+ from the phosphorylated proton pump, thus preventing the K^+-dependent dephosphorylation of H^+,K^+-ATPase.[19] At variance from PPIs, P-CABs are acid stable and not subjected to degradation at the pH levels achievable in the gastric lumen, thereby implying that P-CABs can be administered by oral route without requiring enteric-coated formulations.[20] Moreover, P-CABs achieve rapidly peak plasma levels after oral administration, thus allowing a rapid blockade of H^+,K^+-ATPase in its mid-cycle, without

requiring proton pump activation, which is instead mandatory for PPIs.[21] As a consequence of these molecular pharmacodynamic properties, P-CABs display a faster onset of acid inhibitory action and elevation of gastric pH than PPIs, reaching a full antisecretory effect since the first dose, within the first day of therapy.[22] Furthermore, their control on gastric pH throughout the 24-hour period is more stable than PPIs, and the duration of their antisecretory effect is related to their plasma elimination half-life (t½).[20]

Several candidate compounds acting as P-CABs have been developed with the aim of identifying a suitable drug for treatment of acid-related diseases. However, most of them have been discontinued in the clinical phase of development, owing to their insufficient efficacy (i.e., short duration of action) or hepatic toxicity.[23-25] Recently, Takeda Pharmaceutical Company Limited (Japan) developed a novel and potent P-CAB (vonoprazan), endowed with a different chemical structure and pharmacological performance than previous compounds of the class, with the goal of overcoming their shortcomings.

3. Vonoprazan, a new H^+,K^+-ATPase inhibitor acting as a P-CAB

Vonoprazan is an acid-resistant pyrrole derivative, 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (Box 1), characterized by a rapid, potent, stable and long-lasting acid inhibitory effect resulting from the reversible inhibition of gastric proton pump via competition with K^+ binding on the luminal surface of H^+,K^+-ATPase.[26] In a recent review, we examined in detail the available studies documenting the pharmacodynamics and pharmacokinetics of vonoprazan, including investigations on *in vitro* and *in vivo* experimental models, studies on healthy volunteers; clinical trials in patients with GERD; comparative studies with PPIs in healthy volunteers and patients with GERD.[10] Therefore, the present section is intended only to provide a summary on the main physico-chemical features and relevant pharmacological properties of

vonoprazan underlying its clinical benefits (Table 2), as compared with PPIs and previous P-CABs.

3.1. Pharmacodynamics

Vonoprazan is a weak base with a higher pKa value (9.3) than previous P-CABs and PPIs. Once exposed to an acidic environment, vonoprazan undergoes protonation instantly. These physico-chemical properties explain why the pharmacodynamic activity of vonoprazan under neutral conditions (pH 7.5) remains almost the same as that recorded at pH 6.5. Moreover, the compound is resistant to strong acidity and these characteristics favor a remarkable accumulation of vonoprazan within the canalicula of gastric parietal cells, where it achieve concentrations up to 10^8-fold higher than in the blood (pH 7.4) and remains in its protonated form, which binds and inhibits the proton pumps.[26, 27]

Vonoprazan is highly selective for binding to the H^+,K^+-ATPase,[28] and exerts a potent blocking activity on gastric proton pumps even in a neutral environment, with an inhibitory constant (K_i) of 10 nM at pH 7 and 3 nM at pH 6.5.[26] This P-CAB was found to accumulate in both resting and stimulated gastric glands more than lansoprazole, thus indicating that it is the high affinity of vonoprazan that determines its binding selectivity, and not the pH within the canalicular compartment.[29, 30] Under *in vitro* conditions, the binding rate of vonoprazan reaches the plateau of inhibition within 200 s. However, such a slow onset of action does not appear to affect its efficacy on diurnal pH control *in vivo*.[26, 27] Vonoprazan was confirmed to be a more potent inhibitor of gastric proton pump than the prototype P-CAB, SCH28080, and lansoprazole; indeed, the *in vitro* half-maximal inhibitory concentrations (IC_{50}) were 0.019 nM, 0.14 nM, and 7.6 µM, respectively.[26] As an additional advantage, the dissociation rate of vonoprazan from proton pumps is slower than other P-CABs, this property accounting for a longer duration of its acid inhibitory activity.

The dissociation half-life of vonoprazan is 7.5 hours in isolated proton pumps, as compared with <2 min of SCH28080.[26]

Overall, according to studies in preclinical models, vonoprazan displays a slightly slower onset of action, while displaying higher affinity for gastric H^+,K^+-ATPase and a slower dissociation rate, as compared to previous P-CABs. These unique pharmacological properties may account for its more potent, stable and longer-lasting gastric acid inhibition. In support of this view, *in vivo* preclinical tests and studies on healthy volunteers have shown that single oral doses of vonoprazan can exert a more intense and sustained gastric antisecretory activity than previous P-CABs and PPIs.[15, 27, 31-35] In particular, vonoprazan increases intragastric pH above 4.0 as early as 4 hours after an oral dose of 20 mg, and maintains an extensive antisecretory effect up to 24 hours post-dosing.[15] Moreover, a recent study in healthy Japanese volunteers showed that intragastric pH greater than 5 holding time ratio was 99% with vonoprazan 20 mg twice daily and 84% with esomeprazole 20 mg twice daily when administered for 7 days.[35] In the same study, consistently with previous reports, the acid inhibitory effect of vonoprazan was higher than that of esomeprazole.[35]

3.2 Pharmacokinetics

Being acid resistant, vonoprazan can be given as an oral rapid-release formulation.[36] In phase I studies, conducted on healthy male subjects in Japan and UK, plasma concentration–time profiles of vonoprazan at all dose levels were consistent with a pattern of rapid absorption (median T_{max} up to 2 hours) under fasting conditions, with an estimated $t_{½}$ up to 9 hours. The systemic exposure (i.e., the maximum observed concentration, C_{max}, and bioavailability, area under the plasma concentration-time curve, AUC) was slightly higher than dose proportional. Overall, no clear difference in vonoprazan pharmacokinetics was observed between Japanese and non-Japanese subjects.[15, 33]

Recently, *in vitro* and *in vivo* preclinical studies on the metabolism of vonoprazan revealed that multiple hepatic metabolic enzymes, including oxidation, and sulfation pathways (i.e., CYP3A4, CYP2B6, CYP2C19, CYP2D6, and the non-CYP enzyme SULT2A1) are the major routes of clearance for the parent compound and its metabolites.[37, 38] Of note, CYP2C19 gene polymorphisms have been shown to influence the pharmacokinetics of some PPIs, thus generating relevant inter-individual variability of their pharmacodynamics and clinical activity.[39] Conversely, vonoprazan metabolism displays a limited influence by CYP polymorphisms. In particular, studies on both healthy male volunteers and GERD patients have shown that the pharmacokinetics and pharmacodynamics of vonoprazan are not affected by the CYP2C19 genotype.[15, 32-35, 40] Furthermore, a phase I study investigated the effect of multiple oral doses of the potent CYP3A4 inhibitor clarithromycin on the pharmacokinetics of a single oral dose of vonoprazan 40 mg, showing the absence of any clinically significant pharmacokinetic interaction.[41]

4. Efficacy of vonoprazan in *H. pylori* eradication

Eradication therapy for *H. pylori* infection is based currently on a combination of at least two antibiotics and one gastric acid suppressant to elevate the intragastric pH to 5 or above, thus facilitating *H. pylori* transition from a stationary phase to a growth phase, which increases the susceptibility of bacteria more to antibiotics.[42, 43] For decades, conventional PPIs have been used to suppress gastric acid secretion during *H. pylori* eradication. Recently, however, the eradication rates are displaying a trend to decrease, due to the growing resistance of *H. pylori* to the antibiotics used in treatment regimens.[8, 9] Since the eradication rate correlates well with the degree of acid inhibition, the development of a new drug, such as vonoprazan, endowed with a long duration of action, along with a rapid, stable and strong inhibition of gastric acid secretion, has gained a growing clinical attention. Notably, in Japan, vonoprazan

has been approved for eradication of *H. pylori* as one of the first-line therapies in combination with amoxicillin and clarithromycin, and as a second-line therapy in combination with amoxicillin and metronidazole.[16]

Several retrospective studies have shown that *H. pylori* eradication rates with vonoprazan-based first-line triple therapy were higher than with PPI-based therapy (including rabeprazole, lansoprazole or esomeprazole), ranging from 83% to 92% versus 57% to 76%.[44-50] Of note, these studies reported wide ranges of eradication rates for therapies based both on vonoprazan and traditional PPIs, thus suggesting that the underlying source of variability was not intrinsic to drugs, but reflected likely other limitations, with particular regard for the retrospective experimental design. Along the same line, in the setting of first eradication in patients allergic to penicillin, a 7-day triple therapy consisting of clarithromycin, metronidazole and vonoprazan raised the efficacy significantly and allowed a higher eradication rate (vonoprazan 92.9% versus PPI 46.2%).[51] In the same study, a 7-day regimen consisting of metronidazole and sitafloxacin was effective in patients allergic to penicillin who received either PPI or vonoprazan, with or without past failure of eradication.[51] Of note, Noda et al.[49] investigated how the presence of clarithromycin-resistant strains might influence the eradication success, showing that both in the clarithromycin-sensitive and clarithromycin-resistant subgroups, the eradication rates were significantly higher in patients receiving vonoprazan-based therapy than those receiving PPIs. Likewise, Matsumoto et al.[50] showed that the eradication rates with clarithromycin-resistant *H. pylori* strains were 76.1% versus 40.2% for vonoprazan and PPIs, respectively. In a randomized, double-blind, phase III clinical study comparing *H. pylori* eradication therapies, a total of 650 patients were randomized to first-line triple therapy (based on amoxicillin 750 mg and clarithromycin 200 or 400 mg twice daily for 7 days) with either vonoprazan 20 mg, or lansoprazole 30 mg. The eradication rate was 92.6% in the vonoprazan group and 75.9% in

the lansoprazole group. Notably, in post-hoc analyses, the *H. pylori* eradication rate was significantly higher with vonoprazan as compared with lansoprazole in patients infected with clarithromycin-resistant strains (82% and 40%, respectively), as well as among CYP2C19 extensive metabolizers (92.9% and 75%, respectively).[52]

At present, the efficacy of vonoprazan, in comparison with PPIs, after *H. pylori* eradication failure with first-line treatment remains largely unknown. Vonoprazan has been shown to be highly effective (eradication rate 98%) as a component of second-line triple therapy with amoxicillin and metronidazole in patients failing vonoprazan-based or lansoprazole-based first-line triple therapy.[52] On the other hand, two retrospective comparative studies investigated the success rate for *H. pylori* eradication of vonoprazan-based second-line triple therapy, showing similar eradication rates to those achieved with PPI-based therapy.[46, 48] Interestingly, in a prospective cohort study, Inaba et al.[53] investigated the effects of a 1-week treatment with amoxicillin, clarithromycin and vonoprazan, as second-line treatment in patients with failure after first-line 1-week treatment with rabeprazole, amoxicillin and clarithromycin. The results showed that, in 70.2% of cases with failure after rabeprazole-based therapy, an eradication was achieved with vonoprazan-based therapy (data reported only in a published letter).

5. Efficacy of vonoprazan in patients with other acid-related diseases

Vonoprazan has been approved in Japan for treatment of acid-related diseases, including GERD, erosive esophagitis, PUD, and NSAID-associated upper GI adverse events.[16, 36] This section aims at summarizing the main data, to discuss whether the favorable pharmacological profile of vonoprazan actually translates into greater clinical benefits in patients with acid-related disorders, particularly as compared with current PPI therapies.

5.1 GERD and erosive esophagitis

A phase III, randomized, double-blind, placebo-controlled, multicenter study, compared vonoprazan and placebo with respect to the frequency and severity of heartburn in patients with non-erosive reflux disease. The authors concluded that vonoprazan at doses of 10 and 20 mg was not superior to placebo with respect to the proportion of days without heartburn, whereas the mean severity of heartburn was lower with vonoprazan as compared with placebo.[54] However, a relevant limitation of this study was the inclusion of several patients with possibly confounding conditions (i.e., patients with functional dyspepsia or functional heartburn).[54]

With regard for erosive esophagitis, Ashida et al.[40, 55] performed two phase II, multicenter, randomized, double-blind, parallel-group studies in Japanese patients with endoscopically confirmed erosive esophagitis (Los Angeles Classification grades A-D). The first study was designed to evaluate the efficacy of once-daily vonoprazan (5, 10, 20 or 40 mg) versus once-daily lansoprazole (30 mg) in erosive esophagitis healing. They observed that vonoprazan was effective and non-inferior to lansoprazole in healing esophagitis at all tested doses. Of interest, the healing rate after two weeks of treatment with vonoprazan 20 mg was higher than with lansoprazole 30 mg (90.7% versus 81.9%, P <0.0001) and the difference between the two groups was 8.8% (95% CI: 2.105–15.448).[40] The second study was aimed at confirming the non-inferiority of vonoprazan 20 mg/day versus lansoprazole 30 mg/day in patients with erosive esophagitis, and then to assess the long-term efficacy of vonoprazan as maintenance therapy. In this study, vonoprazan and lansoprazole were found to be equally effective at 8 weeks. However, it is worth noting that there was a higher proportion of healed patients at week 2 in the vonoprazan group (90.7% versus 81.9%). Moreover, in a post-hoc analysis, the stratification of patients according to Los Angeles Classification revealed a higher proportion of healing in the vonoprazan group, as compared with lansoprazole, in

patients with more severe esophagitis (grades C/D), as well as in those classified as CYP2C19 extensive metabolizers. Subsequently, patients with healing at 8 weeks were randomized to receive vonoprazan 10 or 20 mg/day as maintenance therapy up to 52 weeks. Over this period, the recurrence rate of erosive esophagitis was low (<10%).[55] At last, in both studies, an improvement in the severity and frequency of symptoms was reported in both the vonoprazan and lansoprazole groups, without significant differences among the treatment groups.[40, 55]

5.2 Gastric and duodenal ulcers

Two randomized, controlled trials were carried out to evaluate the non-inferiority of vonoprazan versus lansoprazole for treatment of gastric or duodenal ulcer. Most of the enrolled patients were positive for *H. pylori* serology (82.8% and 79.4%, respectively, both in the gastric and duodenal ulcer groups). The non-inferiority of vonoprazan to lansoprazole with respect to the endoscopic healing of gastric ulcers during 8 weeks of treatment was confirmed (93.5% versus 93.8% for vonoprazan and lansoprazole, respectively). Conversely, although the healing rates in both treatment groups were similar, non-inferiority was not achieved with respect to endoscopic healing of duodenal ulcers during 6 weeks of treatment (95.5% versus 98.3% for vonoprazan and lansoprazole, respectively). The most likely explanation for such a difference was supposed to be the number of patients with early discontinuation of treatment in the duodenal ulcer study. Indeed, 7 patients in the vonoprazan group and 2 patients in the lansoprazole group discontinued treatment early without confirmation of duodenal ulcer healing, and were therefore considered as non-healed for the analysis. With regard to *H. pylori* infection, subgroup analyses showed similar healing rates in both H. pylori-positive and -negative patients, both in gastric and duodenal ulcer groups.[56]

6. Safety profile of vonoprazan

Initially, the safety and tolerability of vonoprazan have been investigated in phase I studies on healthy male volunteers. In these settings, vonoprazan was safe and well tolerated at all tested doses, as compared with placebo or PPIs.[15, 33, 34]

In a phase III study, where vonoprazan was administered as a part of a first-line triple therapy for *H. pylori* eradication, Murakami et al.[52] showed comparable rates of treatment-emergent adverse events (TEAEs) for vonoprazan and lansoprazole. Subsequently, in patients allocated to receive second-line vonoprazan-based triple therapy as an open-label treatment, vonoprazan displayed an overall safe profile. Of note, in both first-line and second-line eradication phases, serum gastrin levels increased after vonoprazan administration. However, gastrin levels returned to basal pre-administration levels after completion of either first-line or second-line triple therapy.[52] On the other hand, one case of erythema multiforme, which required oral steroid treatment, was reported during the first-line treatment with vonoprazan.[57] Moreover, a retrospective study by Suzuki et al.[44] showed that the incidence of skin rashes was significantly higher with the vonoprazan-based than PPI-based triple therapy. However, no patients discontinued *H. pylori* eradication treatment or were hospitalized due to the occurrence of adverse events, including skin rashes.[44]

The safety profile of vonoprazan was evaluated also in patients with erosive esophagitis, and it was found to be safe and well tolerated at all the investigated doses (5, 10, 20 and 40 mg once daily for 8 weeks, and 10 and 20 mg once daily for 52 weeks).[40, 55] However, higher increments of serum gastrin were observed during treatment with vonoprazan, as compared with lansoprazole.[40]

In patients with gastric or duodenal ulcers, the incidence of TEAEs was slightly lower for gastric ulcer and slightly higher for duodenal ulcer with vonoprazan than lansoprazole. It is worth noting that there was one death (subarachnoid haemorrhage) in the vonoprazan group

with duodenal ulcer. The possibility of a relationship between this unexpected death and the drug treatment could not be ruled out. In both studies, the increments of serum gastrin levels were higher in vonoprazan-treated versus lansoprazole-treated patients; levels returned to baseline after the end of treatment in both groups.[56]

7. Conclusions

Traditional PPIs, which are endowed with benzimidazole structure and act as irreversible blockers of H^+K^+-ATPase, are currently regarded as first-line drugs for the therapeutic management of acid-related diseases. However, despite their well-documented clinical efficacy and safety, PPIs display a number of limitations and unmet clinical needs that have prompted the development of novel drugs to improve the outcomes of acid-related diseases, including the eradication of *H. pylori*. In this context, P-CABs have been identified as novel drugs able to inhibit gastric acid secretion through a reversible blockade of the gastric proton pump. So far, vonoprazan is the only P-CAB approved in Japan for clinical use. At variance with PPIs, vonoprazan has been claimed to ensure an inhibition of gastric acid secretion characterized by fast onset, higher magnitude and long-lasting persistence. This drug has been shown to compete with K^+ binding on the proton pump, and to induce a selective and reversible inhibition of H^+-K^+-ATPase in a dose-dependent manner. Studies in preclinical models and humans have documented the ability of vonoprazan of inhibiting gastric proton pumps more effectively than previous P-CABs and PPIs. In particular, vonoprazan is endowed with a higher pKa than previous P-CABs and PPIs. Therefore, it is stable in acid environments and is subject to high concentration within the secretory canalicula of gastric parietal cells, where it binds and inhibits proton pumps. Of note, at variance from PPIs, the acid inhibitory effect of vonoprazan does not require proton pump activation and it is unaffected by the gastric secretory activity. Consistently with these patterns, vonoprazan has

been shown to display some advantages over PPIs: more rapid onset of action, more stable and powerful elevation of gastric pH, particularly during nightime, and longer-lasting inhibitory effect on gastric acid secretion. The specific advantages of vonoprazan, as compared to previous P-CABs, include a slower dissociation rate from the H^+,K^+-ATPase, that accounts for a longer duration of action, and the lack of hepatotoxicity that has precluded the clinical use of P-CABs.

As a consequence of the above physico-chemical and pharmacological properties, human studies have shown that vonoprazan can exert its full antisecretory activity since administration of the first dose and provides a sustained control of acid secretion, including the nocturnal period. Furthermore, at variance with most of currently available PPIs, the metabolic disposition of vonoprazan is not significantly influenced by CYP2C19 genetic polymorphism, thus resulting in a low interindividual variability. Whether these favorable pharmacological properties will translate into greater clinical benefits in patients with acid-related disorders, as compared with PPI therapy, remains to be established conclusively. Recent evidence suggests that vonoprazan can be preferred to PPIs as maintenance therapy for reflux esophagitis and eradication of *H. pylori* owing to its stronger antisecretory effect. Moreover, vonoprazan displays favorable safety and tolerability profiles, even though long-term studies on the effects of vonoprazan are required.

8. Expert opinion

Currently available PPIs represent the mainstay for therapeutic management of acid-related disorders. However, despite their undoubted benefits, there are still some unmet clinical needs, partly due to their suboptimal pharmacological profiles, that deserve consideration and wait for adequate solutions. These include mainly: the management of patients with reflux symptoms who do not respond adequately to PPI therapy; the need for a faster onset of

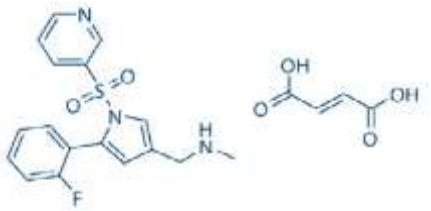
symptom relief; the optimization of acid inhibition with regard for the daily time course of gastric pH control, particularly over the night. Moreover, it is worth noting that the eradication rates of *H. pylori* with first-line treatments has recently suffered of a significant drop. In this context, an innovative approach has been the development of a new class of H^+,K^+-ATPase inhibitors, designated as P-CABs, among which vonoprazan has been approved in Japan for treatment of acid-related diseases, including GERD, erosive esophagitis, PUD, NSAID-associated upper GI adverse events, and *H. pylori* eradication.

Clinical and pharmacological investigations have demonstrated that vonoprazan is able to exert a direct and targeted effect on parietal cells, providing a rapid, potent and long-lasting inhibition of acid secretion, including a better nighttime control. Furthermore, as compared with some PPIs, the metabolic pathway of vonoprazan is unaffected by CYP2C19 genotype, allowing for less inter-individual antisecretory variability. Since the onset of acid inhibition occurs irrespectively of the functional status of proton pumps, vonoprazan does not require any specific timing with respect to food intake. At last, as vonoprazan is stable in acidic environments, no enteric coating is required to prevent it from degradation in the acidic environment of the gastric lumen. Overall, these unique properties of vonoprazan should promise an improved management of acid-related diseases, particularly in patients unresponsive to PPIs.

The results of trials in Japanese patients with erosive esophagitis have shown that the healing rate after two weeks of treatment with vonoprazan was higher than lansoprazole, with a higher trend to achieve healing among patients with more severe esophagitis in the vonoprazan group. However, given the limited clinical data available on vonoprazan, additional and more extensive randomized controlled clinical trials are urgently required to confirm its actual advantages for both short- and long-term maintenance of GERD patients, with and without erosive esophagitis, as well as in patients affected by other acid-related diseases. Indeed, since

not all acid-related disorders require strong acid inhibition, the clinical relevance of vonoprazan-based therapies awaits verification in large-scale comparative clinical studies. In particular, special attention should be paid to randomized controlled trials evaluating the putative effectiveness of vonoprazan in patients with refractoriness to therapy with current PPIs. Given the increasing trend towards a failure of *H. pylori* eradication with PPI-based regimens, vonoprazan deserves a special clinical attention in this area. Indeed, it has been estimated that to achieve an adequate antimicrobial potency in *H. pylori* eradication therapy, luminal gastric pH values above 5 are required to promote the transition of *H. pylori* into its proliferative phase. In this respect, recent studies have indicated that eradication failure can be overcome by maintaining elevated gastric pH levels, which can be achieved by vonoprazan use. Moreover, an additional plausible explanation for its efficacy is that, since vonoprazan, amoxicillin, and clarithromycin are metabolized by CYP3A4, their combined administration treatment could result in a clearance delay. However, published data on the efficacy and safety of vonoprazan in the treatment of *H. pylori* infection are still limited and retrospective in the majority of cases. In addition, we deem of interest to implement studies aimed at investigating whether vonoprazan-based triple therapy for *H. pylori* eradication may be more effective than sequential, quadruple or long-term therapy. At last, other areas deserving attention include the safety profile of vonoprazan over long-term treatment periods, as well as the potential interactions of vonoprazan with other drugs. Indeed, since multiple metabolizing enzymes are involved in the primary metabolism of vonoprazan (not only some CYP isoforms), it has been suggested that vonoprazan might be less affected by the concomitant administration of drugs that inhibit or induce these enzymes.

Drug Summary Box

Drug name	Vonoprazan fumarate
Phase	III
Indication	- Acid-related diseases (including gastroesophageal reflux disease and peptic ulcer disease) - Adjunct to *Helicobacter pylori* eradication
Pharmacology description	Potassium-competitive acid blocker (P-CAB)
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	26, 27, 29, 30

REFERENCES

1. Sachs G. Proton pump inhibitors and acid-related diseases. Pharmacotherapy 1997 Jan-Feb;17(1):22-37.
2. Savarino V, Dulbecco P, de Bortoli N, Ottonello A, Savarino E. The appropriate use of proton pump inhibitors (PPIs): Need for a reappraisal. European journal of internal medicine 2017 Jan;37:19-24.
3. Kahrilas PJ, Shaheen NJ, Vaezi MF, American Gastroenterological Association I, Clinical P, Quality Management C. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology 2008 Oct;135(4):1392-413, 413 e1-5.
4. Martinucci I, de Bortoli N, Savarino E, Nacci A, Romeo SO, Bellini M, et al. Optimal treatment of laryngopharyngeal reflux disease. Therapeutic advances in chronic disease 2013 Nov;4(6):287-301.
5. Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD An overview of their pharmacology, efficacy and safety. Pharmacological research 2009 Mar;59(3):135-53.
6. Scarpignato C, Pelosini I, Di Mario F. Acid suppression therapy: where do we go from here? Digestive diseases 2006;24(1-2):11-46.
7. Hershcovici T, Fass R. Management of gastroesophageal reflux disease that does not respond well to proton pump inhibitors. Current opinion in gastroenterology 2010 Jul;26(4):367-78.
8. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut 2010 Aug;59(8):1143-53.
9. Megraud F. The challenge of Helicobacter pylori resistance to antibiotics: the comeback of bismuth-based quadruple therapy. Therapeutic advances in gastroenterology 2012 Mar;5(2):103-9.
10. Savarino E, Martinucci I, Furnari M, Romana C, Pellegatta G, Moscatelli A, et al. Vonoprazan for treatment of gastroesophageal reflux: pharmacodynamic and pharmacokinetic considerations. Expert opinion on drug metabolism & toxicology 2016 Aug 08:1-9.
11. Savarino V, Savarino E, Dulbecco P. Proton pump inhibitor failure: why does it occur and how can it be managed? Digestion 2006;73(4):215-7.
12. de Bortoli N, Martinucci I, Giacchino M, Blandizzi C, Marchi S, Savarino V, et al. The pharmacokinetics of ilaprazole for gastro-esophageal reflux treatment. Expert opinion on drug metabolism & toxicology 2013 Oct;9(10):1361-9.
13. Savarino E, Ottonello A, Martinucci I, Dulbecco P, Savarino V. Ilaprazole for the treatment of gastro-esophageal reflux. Expert opinion on pharmacotherapy 2016 Oct;17(15):2107-13.
14. Dutta U, Armstrong D. Novel pharmaceutical approaches to reflux disease. Gastroenterology clinics of North America 2013 Mar;42(1):93-117.
15. Jenkins H, Sakurai Y, Nishimura A, Okamoto H, Hibberd M, Jenkins R, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Alimentary pharmacology & therapeutics 2015 Apr;41(7):636-48.
*This study evaluates the pharmacological effects of vonoprazan
16. Garnock-Jones KP. Vonoprazan: first global approval. Drugs 2015 Mar;75(4):439-43.
17. Munson KB, Sachs G. Inactivation of H+,K+-ATPase by a K+-competitive photoaffinity inhibitor. Biochemistry 1988 May 31;27(11):3932-8.

18. Mendlein J, Sachs G. Interaction of a K(+)-competitive inhibitor, a substituted imidazo[1,2a] pyridine, with the phospho- and dephosphoenzyme forms of H+, K(+)-ATPase. The Journal of biological chemistry 1990 Mar 25;265(9):5030-6.
19. Parsons ME, Keeling DJ. Novel approaches to the pharmacological blockade of gastric acid secretion. Expert opinion on investigational drugs 2005 Apr;14(4):411-21.
20. Andersson K, Carlsson E. Potassium-competitive acid blockade: a new therapeutic strategy in acid-related diseases. Pharmacology & therapeutics 2005 Dec;108(3):294-307.
21. Wurst W, Hartmann M. Current status of acid pump antagonists (reversible PPIs). The Yale journal of biology and medicine 1996 May-Jun;69(3):233-43.
22. Simon WA, Herrmann M, Klein T, Shin JM, Huber R, Senn-Bilfinger J, et al. Soraprazan: setting new standards in inhibition of gastric acid secretion. The Journal of pharmacology and experimental therapeutics 2007 Jun;321(3):866-74.
23. Ene MD, Khan-Daneshmend T, Roberts CJ. A study of the inhibitory effects of SCH 28080 on gastric secretion in man. British journal of pharmacology 1982 Jul;76(3):389-91.
24. Dent J, Kahrilas PJ, Hatlebakk J, Vakil N, Denison H, Franzen S, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. The American journal of gastroenterology 2008 Jan;103(1):20-6.
25. Kim HK, Park SH, Cheung DY, Cho YS, Kim JI, Kim SS, et al. Clinical trial: inhibitory effect of revaprazan on gastric acid secretion in healthy male subjects. Journal of gastroenterology and hepatology 2010 Oct;25(10):1618-25.
26. Shin JM, Inatomi N, Munson K, Strugatsky D, Tokhtaeva E, Vagin O, et al. 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-methylmethanamin e monofumarate (TAK-438). The Journal of pharmacology and experimental therapeutics 2011 Nov;339(2):412-20.
27. Hori Y, Imanishi A, Matsukawa J, Tsukimi Y, Nishida H, Arikawa Y, et al. 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamin e monofumarate (TAK-438), a novel and potent potassium-competitive acid blocker for the treatment of acid-related diseases. The Journal of pharmacology and experimental therapeutics 2010 Oct;335(1):231-8.
28. Matsukawa J, Kogame A, Tagawa Y, Inatomi N. Radiographic Localization Study of a Novel Potassium-Competitive Acid Blocker, Vonoprazan, in the Rat Gastric Mucosa. Digestive diseases and sciences 2016 Jul;61(7):1888-94.
29. Matsukawa J, Hori Y, Nishida H, Kajino M, Inatomi N. A comparative study on the modes of action of TAK-438, a novel potassium-competitive acid blocker, and lansoprazole in primary cultured rabbit gastric glands. Biochemical pharmacology 2011 May 1;81(9):1145-51.
30. Scott DR, Munson KB, Marcus EA, Lambrecht NW, Sachs G. The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+ -ATPase. Alimentary pharmacology & therapeutics 2015 Dec;42(11-12):1315-26.
31. Hori Y, Matsukawa J, Takeuchi T, Nishida H, Kajino M, Inatomi N. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. The Journal of pharmacology and experimental therapeutics 2011 Jun;337(3):797-804.
32. Arikawa Y, Nishida H, Kurasawa O, Hasuoka A, Hirase K, Inatomi N, et al. Discovery of a novel pyrrole derivative 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamin e fumarate (TAK-438) as a potassium-competitive acid blocker (P-CAB). Journal of medicinal chemistry 2012 May 10;55(9):4446-56.

33. Sakurai Y, Nishimura A, Kennedy G, Hibberd M, Jenkins R, Okamoto H, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Rising TAK-438 (Vonoprazan) Doses in Healthy Male Japanese/non-Japanese Subjects. Clinical and translational gastroenterology 2015;6:e94.
34. Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects--a randomised open-label cross-over study. Alimentary pharmacology & therapeutics 2015 Sep;42(6):719-30.
* This randomized, comparative, cross-over study demonstrates that vonoprazan exerts a more rapid and sustained acid-inhibitory effect compared to the second generation of PPIs (esomeprazole or rabeprazole)
35. Kagami T, Sahara S, Ichikawa H, Uotani T, Yamade M, Sugimoto M, et al. Potent acid inhibition by vonoprazan in comparison with esomeprazole, with reference to CYP2C19 genotype. Alimentary pharmacology & therapeutics 2016 May;43(10):1048-59.
* Differently from Esomeprazole, this study shows that the acid-inhibitoy effect of vonoprazan is not significantly influenced by the CYP2C19 genetic polymorphisms
36. Echizen H. The First-in-Class Potassium-Competitive Acid Blocker, Vonoprazan Fumarate: Pharmacokinetic and Pharmacodynamic Considerations. Clinical pharmacokinetics 2016 Apr;55(4):409-18.
37. Kogame A, Takeuchi T, Nonaka M, Yamasaki H, Kawaguchi N, Bernards A, et al. Disposition and metabolism of TAK-438 (vonoprazan fumarate), a novel potassium-competitive acid blocker, in rats and dogs. Xenobiotica; the fate of foreign compounds in biological systems 2017 Mar;47(3):255-66.
38. Yamasaki H, Kawaguchi N, Nonaka M, Takahashi J, Morohashi A, Hirabayashi H, et al. In vitro metabolism of TAK-438, vonoprazan fumarate, a novel potassium-competitive acid blocker. Xenobiotica; the fate of foreign compounds in biological systems 2016 Jul 14:1-8.
39. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug metabolism and pharmacokinetics 2005 Jun;20(3):153-67.
40. Ashida K, Sakurai Y, Nishimura A, Kudou K, Hiramatsu N, Umegaki E, et al. Randomised clinical trial: a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the treatment of erosive oesophagitis. Alimentary pharmacology & therapeutics 2015 Sep;42(6):685-95.
* This study comparing vonoprazan vs lansoprazole in erosive esophagitis patients revealed that the proportion of patients with healed erosive esophagitis tended to be higher in the vonoprazan group, as compared with lansoprazole, in patients with more severe esophagitis (grades C/D) as well as in those classified as CYP2C19 extensive metabolisers.
41. Jenkins H, Jenkins R, Patat A. Effect of Multiple Oral Doses of the Potent CYP3A4 Inhibitor Clarithromycin on the Pharmacokinetics of a Single Oral Dose of Vonoprazan: A Phase I, Open-Label, Sequential Design Study. Clinical drug investigation 2017 Mar;37(3):311-16.
42. Sachs G, Scott DR, Wen Y. Gastric infection by Helicobacter pylori. Current gastroenterology reports 2011 Dec;13(6):540-6.
43. Sugimoto M, Furuta T, Shirai N, Kodaira C, Nishino M, Ikuma M, et al. Evidence that the degree and duration of acid suppression are related to Helicobacter pylori eradication by triple therapy. Helicobacter 2007 Aug;12(4):317-23.
44. Suzuki S, Gotoda T, Kusano C, Iwatsuka K, Moriyama M. The Efficacy and Tolerability of a Triple Therapy Containing a Potassium-Competitive Acid Blocker

Compared With a 7-Day PPI-Based Low-Dose Clarithromycin Triple Therapy. The American journal of gastroenterology 2016 Jul;111(7):949-56.
45. Shinozaki S, Nomoto H, Kondo Y, Sakamoto H, Hayashi Y, Yamamoto H, et al. Comparison of vonoprazan and proton pump inhibitors for eradication of Helicobacter pylori. The Kaohsiung journal of medical sciences 2016 May;32(5):255-60.
46. Yamada S, Kawakami T, Nakatsugawa Y, Suzuki T, Fujii H, Tomatsuri N, et al. Usefulness of vonoprazan, a potassium ion-competitive acid blocker, for primary eradication of Helicobacter pylori. World journal of gastrointestinal pharmacology and therapeutics 2016 Nov 06;7(4):550-55.
47. Shichijo S, Hirata Y, Niikura R, Hayakawa Y, Yamada A, Mochizuki S, et al. Vonoprazan versus conventional proton pump inhibitor-based triple therapy as first-line treatment against Helicobacter pylori: A multicenter retrospective study in clinical practice. Journal of digestive diseases 2016 Oct;17(10):670-75.
48. Sakurai K, Suda H, Ido Y, Takeichi T, Okuda A, Hasuda K, et al. Comparative study: Vonoprazan and proton pump inhibitors in Helicobacter pylori eradication therapy. World journal of gastroenterology : WJG 2017 Jan 28;23(4):668-75.
49. Noda H, Noguchi S, Yoshimine T, Goji S, Adachi K, Tamura Y, et al. A Novel Potassium-Competitive Acid Blocker Improves the Efficacy of Clarithromycin-containing 7-day Triple Therapy against Helicobacter pylori. Journal of gastrointestinal and liver diseases : JGLD 2016 Sep;25(3):283-8.
50. Matsumoto H, Shiotani A, Katsumata R, Fujita M, Nakato R, Murao T, et al. Helicobacter pylori Eradication with Proton Pump Inhibitors or Potassium-Competitive Acid Blockers: The Effect of Clarithromycin Resistance. Digestive diseases and sciences 2016 Nov;61(11):3215-20.
** Randomized, double-blind, phase III clinical study comparing H. pylori eradication therapies, in 650 patients randomized to first-line triple therapy with either vonoprazan 20 mg, or lansoprazole 30 mg.
51. Ono S, Kato M, Nakagawa S, Mabe K, Sakamoto N. Vonoprazan improves the efficacy of Helicobacter pylori eradication therapy with a regimen consisting of clarithromycin and metronidazole in patients allergic to penicillin. Helicobacter 2017 Jan 18.
52. 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.
53. Inaba T, Iwamuro M, Toyokawa T, Okada H. Letter: promising results of Helicobacter pylori eradication with vonoprazan-based triple therapy after failure of proton pump inhibitor-based triple therapy. Alimentary pharmacology & therapeutics 2016 Jan;43(1):179-80.
54. Kinoshita Y, Sakurai Y, Shiino M, Kudou K, Nishimura A, Miyagi T, et al. Evaluation of the Efficacy and Safety of Vonoprazan in Patients with Nonerosive Gastroesophageal Reflux Disease: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. Current therapeutic research, clinical and experimental 2016;81-82:1-7.
* This study compared vonoprazan and placebo with respect to the frequency and severity of heartburn in patients with non-erosive reflux disease.
55. Ashida K, Sakurai Y, Hori T, Kudou K, Nishimura A, Hiramatsu N, et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. Alimentary pharmacology & therapeutics 2016 Jan;43(2):240-51.
* This is the first study comparing vonoprazan vs lansoprazole in erosive esophagitis patients and demonstrating that vonoprazan was effective and non-inferior to lansoprazole in healing esophagitis at low and high doses.

56. Miwa H, Uedo N, Watari J, Mori Y, Sakurai Y, Takanami Y, et al. Randomised clinical trial: efficacy and safety of vonoprazan vs. lansoprazole in patients with gastric or duodenal ulcers - results from two phase 3, non-inferiority randomised controlled trials. Alimentary pharmacology & therapeutics 2017 Jan;45(2):240-52.
* Two randomized, controlled trials were carried out to evaluate the non-inferiority of vonoprazan versus lansoprazole for treatment of gastric or duodenal ulcer.
57. Kamiya K, Nishio E, Horio A, Tokura Y. Erythema multiforme caused by triple therapy with amoxicillin, clarithromycin and vonoprazan for Helicobacter pylori. The Journal of dermatology 2016 Mar;43(3):340-1.

Table 1: Shortcomings and limitations of proton pump inhibitors

Suboptimal pharmacological profiles
• Intake at appropriate time relative to meals • Oral administration as enteric coated formulations • Delay in effect onset (steady-state inhibition of protonic pumps is achieved within 3 to 5 days) • Low bioavailability • Rapid metabolism • Inter-individual variability of pharmacodynamics and clinical activity due to cytochrome polymorphisms • Lack of sustained acid suppression • Nocturnal acid breakthrough • Drug interactions

Table 2: Summary of the main physico-chemical and pharmacological properties of Vonoprazan

- Weak base with high pKa value (9.3)
- Good stability in acid environment (not susceptible to degradation at the low pH levels achievable in the gastric lumen; suitability for formulation as oral fast-release tablets)
- Achievement of high concentrations in the secretory canalicula of parietal cells
- Direct action on H^+,K^+-ATPase (it is not a prodrug and does not requires conversion into pharmacologically active compounds)
- Competitive binding to the potassium binding site of H^+,K^+-ATPase
- Selective, reversible and dose-dependent inhibition of H^+,K^+-ATPase
- Fast onset of the acid inhibitory effect (full antisecretory effect since the first dose)
- Stable and powerful elevation of gastric luminal pH over 24 hours (including the nocturnal period)
- No need for administration before meal (H^+,K^+-ATPase blockade does not require proton pump activation and/or membrane translocation)
- Duration of the acid inhibitory effect related with plasma elimination half-life
- Slow dissociation rate from H^+,K^+-ATPase
- Limited influence by CYP polymorphisms on metabolic disposition (limited inter-individual variability)
- Evidence of efficacy in erosive esophagitis, gastric ulcer and *H. pylori* eradication
- Overall favorable safety profile over the short term