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Potassium-Competitive Acid Blockers: New Opportunities of Antisecretory Therapy in Gastroesophageal Reflux Disease

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Aim: to present modern data on the efficacy and safety of using potassium-competitive acid blockers (P-CAB) using tegoprazan as an example in patients with gastroesophageal reflux disease.
Key points. Potassium-competitive blockers of hydrochloric acid secretion, according to clinical studies, have demonstrated high clinical efficacy and safety in patients with gastroesophageal reflux disease. The advantages of this class of drugs include a faster and longer-lasting antisecretory effect, which does not depend on food intake, as well as the absence of the influence of genetic polymorphisms of the CYP2C19 isoenzyme on pharmacokinetics and the risk of drug interactions. In patients with nocturnal heartburn, the potassium-competitive acid blocker tegoprazan may be the drug of choice to achieve a faster and longer-lasting clinical effect and improve sleep quality. Tegoprazan is effective against nocturnal acid breakthroughs. In several studies, tegoprazan was superior to placebo and proton pump inhibitors (PPIs) in eliminating major symptoms in patients with nonerosive reflux disease and to PPIs in treating erosive esophagitis. P-CABs are considered the drugs of choice in the treatment of gastroesophageal reflux disease refractory to PPIs.
Conclusion. Further studies are needed, including in the Russian Federation, to confirm the high efficacy and safety of tegoprazan.
Keywords: potassium-competitive acid blockers, tegoprazan, gastroesophageal reflux disease, erosive esophagitis, nocturnal heartburn
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Калий-конкурентные блокаторы кислотной продукции: новые возможности антисекреторной терапии гастроэзофагеальной рефлюксной болезни

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Цель обзора: представить современные данные об эффективности и безопасности применения калий-конкурентных блокаторов кислотной продукции (К-КБК) на примере тегопразана у пациентов с гастроэзофагеальной рефлюксной болезнью.
Основные положения. Калий-конкурентные блокаторы секреции соляной кислоты по данным проведенных клинических исследований продемонстрировали высокую клиническую эффективность и безопасность у пациентов с гастроэзофагеальной рефлюксной болезнью. Преимуществами данного класса препаратов служат более быстрый и продолжительный антисекреторный эффект, который не зависит от приема пищи, а также отсутствие влияния генетических полиморфизмов изофермента CYP2C19 на фармакокинетику и риска межлекарственных взаимодействий. У пациентов с ночной изжогой представитель К-КБК тегопразан может быть препаратом выбора для достижения более быстрого и продолжительного клинического эффекта и улучшения качества сна. Тегопразан эффективен в отношении ночных кислотных прорывов. В ряде исследований тегопразан превосходил плацебо и ингибиторы протонной помпы (ИПП) в отношении устранения основных симптомов у больных неэрозивной рефлюксной болезнью и ИПП при лечении эрозивного эзофагита. К-КБК рассматриваются как препараты выбора при лечении гастроэзофагеальной рефлюксной болезни, рефрактерной к ИПП.
Заключение. Необходимо проведение дальнейших исследований, в том числе в Российской Федерации, подтверждающих высокую эффективность и безопасность тегопразана.

Ключевые слова: калий-конкурентные блокаторы кислотной продукции, тегопразан, гастроэзофагеальная рефлюксная болезнь, эрозивный эзофагит, ночная изжога
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Gastroesophageal reflux disease (GERD) remains one of the most common gastrointestinal (GI) diseases worldwide. According to a meta-analysis based on data from 102 studies conducted in 2020, global prevalence of GERD was 13.98 % (95% confidence interval (95% CI): 12.47–15.56) [1]. In the Russian Federation, GERD frequency is steadily increasing, and according to the latest multicenter study, it reaches 34.2 % among the subjects presenting at outpatient clinics [2].

The relevance of GERD problem is related not only to its high prevalence, but also to complications such as esophageal strictures, haemorrhages, Barrett's esophagus (BE), which is a risk factor for esophageal adenocarcinoma (EAC) [3, 4]. According to histopathology data, Barrett's esophagus is revealed in 7.2 % patients with GERD (95% CI: 5.4–9.3) [5]. Not associated with epithelial dysplasia it increases the risk of esophageal adenocarcinoma to 0.2–0.5 % [6]. In patients with Barrett's esophagus, the presence of low- and high-grade dysplasia increases the annual risk to 0.7 and 7 %, respectively. The high prevalence of GERD and obesity are among the reasons for rapid increase of esophageal adenocarcinoma incidence. An analysis of state medical statistics showed that over 10 years, from 2010 to 2020, the increase in the incidence of esophageal adenocarcinoma was 10.18 % [7].

Besides severe complications, GERD symptoms have a negative impact on the quality of life of patients, reduce working performance, require long-term and sometimes lifelong drug administration, as well as surgical treatment, which results in significant social and economic impact.

Studies of the pharmacoeconomic aspects associated with GERD demonstrate both high total direct (appointments, cost of medications, tests, and hospitalization) and indirect costs (number of days with total and partial loss of working productivity). According to reports, the total losses from GERD are estimated at 1.446 billion rubles per year [8]. Losses from complicated GERD, considering the costs of treatment and temporary disability, are estimated at 674.6 million rubles per year.

Nocturnal heartburn has negative impact on the quality of life of patients, resulting in sleep disorders with subsequent decrease in daytime activity and working productivity [9].

Thus, the main goals in the treatment of patients with GERD include alleviation of disease symptoms, healing of erosive esophagitis, prevention of relapses and complications, and improved quality of life of patients.

Challenges and prospects of gastroesophageal reflux disease treatment

Today, proton pump inhibitors (PPIs) are considered as first-line agents in the treatment of acid-related disorders. Despite significant success in using PPIs in patients with GERD, there are still several unresolved issues remain [10]. Firstly, they include refractory disease course (no response to a standard PPI dose administered once daily for 8 weeks) [11]. According to the literature, a complete or partial lack of response to antisecretory therapy is observed in 40–50 % of patients [12, 13]. Despite PPI treatment, 38 % of patients still have residual GERD manifestations, and 47 % require the addition of other medications to their therapy to reduce or relieve symptoms.

The main causes of refractory GERD may be classified into three groups: patient-related, therapy-related, and not related to GERD [11]. The first group includes poor treatment adherence, failure to comply with the time and frequency of drug administration, genetically determined polymorphism of cytochrome P450 isoforms CYP2C19 and CYP3A4, the patient's cytokine profile, obesity, refluxate character (presence of weakly acidic and weakly alkaline refluxes), impaired upper gastrointestinal tract motility, and the esophagus microbiota. The second group includes nocturnal acid breakthroughs, postprandial acid pocket. The reasons for persistent symptoms despite the antisecretory therapy may include other diseases with similar clinical symptoms (achalasia of cardia, eosinophilic esophagitis, Zollinger – Ellison syndrome, radiation, drug-induced or infectious esophagitis, esophageal adenocarcinoma, rumination syndrome, etc.).

Low patient compliance possesses significant problems for physicians of all specialties and an important reason for the treatment failure. It is known that pharmacokinetics of some PPIs depends on the mealtime and the optimal time for drug administration is 30–60 min before meals. This is necessary to achieve the highest PPI blood levels during the period of maximum proton pump stimulation associated with food intake. However, previous studies have shown that 36 % of physicians do not instruct their patients about the time of PPI administration or provide incorrect instructions [14]. Only half of the patients do not violate the treatment regimen for drugs of this group, among others 39 % take PPIs more than 60 min before meals, 30 % — after meals, 28 % — before bedtime, 4 % — as needed [15].

Therapy-related challenges also arise when treating patients with non-erosive GERD, with nocturnal heartburn, severe erosive esophagitis.

Erosive esophagitis is observed in 25–50 % of patients with GERD and may increase the risk of complications such as esophageal stricture and Barrett's esophagus [16]. Even though PPIs are the drugs of choice for treatment of all GERD forms, approximately 10–30 % patients with Grade C/D (according to the Los Angeles classification) esophagitis fail to achieve endoscopic remission within 8 weeks of therapy [17, 18]. In another study, this value is even higher and amounts to approximately 40 % of patients with severe esophagitis treated for 1.1 years [19].

Previously, a positive correlation was demonstrated between the erosive esophagitis healing rate and the proportion of time with intragastric pH > 4.0 [20]. Thus, drugs with the most pronounced and long-lasting antisecretory effect should be preferred for treating patients with severe erosive esophagitis.

70 % of patients taking PPIs experience nocturnal acid breakthrough (NAB) (gastric pH decrease below 4, lasting more than 1 hour) [21]. In some cases, it is accompanied by acidic gastroesophageal refluxes. This phenomenon may lead to nocturnal heartburn, extraesophageal manifestations of GERD during sleep, and presents as an aggravating factor in erosive esophagitis and Barrett's esophagus. Of note, occurrence of a nocturnal acid breakthrough does not depend on the type of PPI taken by the patient. Not all H^+/K^+-ATPases are active in all patients at the time of PPI administration, and these medications do not act on the inactivated H^+/K^+-ATPases, which may explain occurrence of a nocturnal acid breakthrough.

Acid-suppressive therapy is still developing and currently a new promising class of antisecretory drugs, potassium-competitive acid blockers (P-CABs), undergoes extensive studies. Tegoprazan (CJ-12420) is one of the P-CABs representatives.

Mechanism of action of potassium-competitive acid blockers

Tegoprazan is a highly selective gastric proton pump inhibitor, and unlike PPIs, it competitively and reversibly interacts with the ionic K^+-binding domain of H^+/K^+-ATPase. One of the advantages of P-CABs as a new class of acid-suppressive drugs is the lack of need for activation in acidic environment and stability in parietal cell tubules. This results in faster effect and a pronounced inhibition of hydrochloric acid secretion. P-CAB binds to the active and inactive forms of H^+/K^+-ATPase, which results in longer duration of action [22].

Studies of tegoprazan pharmacokinetics and antisecretory activity have shown a dose-dependent antisecretory effect. At single oral administration, rapid drug absorption was observed, and the time to maximum blood concentration (t_{max}) was on average 1 h (0.5 to 1.5 h) [22, 23].

Dose-dependent antisecretory activity and rapid onset of action were demonstrated by N. Takahashi et al. [24]. Tegoprazan oral administration to dogs at the dose of 1.0 mg/kg resulted in complete inhibition of histamine-induced gastric secretion of hydrochloric acid after 60 min. After tegoprazan administration at the dose of 1 mg/kg, percentage of time with gastric pH > 4 was 54 %, and after administration at the dose of 3 mg/kg it was 89 %.

Tegoprazan has effect on gastric motility, as was demonstrated by the authors of this work, which is a matter of interest and requires further studies. Tegoprazan oral administration at the dose of 3 mg/kg to a dog resulted in resumption of the migrating motor complex phase III after its inhibition with pentagastrin [24].

An important characteristic of the new molecule is the independence of its pharmacokinetics from food intake. After administration of single dose 200 mg tegoprazan after meal or at fasting, median gastric pH was 5.71 and 5.41, respectively, according to 24-hour pH-metry [25]. The time share with gastric pH > 4 was also comparable (85.7 % and 74.4 %, respectively).

The area under the 'concentration — time' curve from the time 0 to the last measurable plasma concentration at the time point t ($AUC_{(0-t)}$) and t1/2 of the compounds were comparable,

although plasma C_{max} of tegoprazan and its metabolite M1 were decreased by 47 % after meal, compared to 43 % at fasting. Thus, no clinically relevant effect of food intake on the drug absorption was observed.

Another advantage of P-CABs is absence of CYP2C19 phenotype effect ("fast", "intermediate", "slow" metabolizers) on tegoprazan pharmacokinetics and clinical efficacy [26]. A randomized clinical trial by E. Yang et al. has shown a rapid increase in intragastric pH > 4 based on daily pH-metry after administration 50 mg tegoprazan at bedtime, compared to PPI and vonoprazan. Percentage of time with pH > 4 after tegoprazan administration was significantly higher, 66 %, compared to 36.1 % for PPI and 60.5 % for vonoprazan. This study has demonstrated not only a more pronounced nocturnal acid breakthrough inhibition by P-CAB compared to PPI, but also the absence of CYP2C19 phenotype effect on the duration and level of acid suppression [26].

To date, data on anti-inflammatory properties of tegoprazan have been obtained. *In vitro* use of tegoprazan 100 μg/mL resulted in decreased proinflammatory cytokines (interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNF-α)) expression and increased anti-inflammatory cytokine (IL-4, IL-10, transforming growth factor β (TGF-β)) gene expression [27]. Decreased nitric oxide production by cells and stimulation of macrophage differentiation to the M2 phenotype, which contribute to the production of anti-inflammatory cytokines, tissue remodeling and repair, were also observed.

Tegoprazan anti-inflammatory effects in patients with GERD were confirmed in a study by S.Y. Kim et al [28]. Tegoprazan 30 μmol/L significantly inhibited the expression of proinflammatory cytokines (IL-6, IL-8, IL-1b, TNF-α) in normal esophageal epithelial cells (Het-1A) treated with hydrochloric acid.

Tegoprazan safety profile, including hepatotoxicity (liver toxic injury, hepatitis, hepatic failure, liver transplantation and other hepatic diseases), was studied in a large retrospective population-based cohort study including 50 million subjects in South Korea [29]. Tegoprazan use was not associated with a higher risk of hepatotoxicity compared to six PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) (risk ratios (RRs): 0.70 (95% CI: 0.69–0.72), 0.81 (0.79–0.83), 0.61 (0.59–0.63), 1.17 (1.13–1.20), 0.61 (0.59–0.62), and 0.73 (0.71–0.75), respectively). Hazard ratio (HR) for tegoprazan compared to six available PPIs was 0.73 (95% CI: 0.72–0.75). Moreover, it was noted that tegoprazan treatment reduced the risk of hepatotoxicity by approximately 27 % compared to PPIs.

Evidence base for tegoprazan efficacy in gastroesophageal reflux disease

Tegoprazan demonstrated high clinical efficacy in patients with nocturnal heartburn. In a double-blind randomized study conducted by J.S. Kim et al., the proportion of heartburn-free nights over 14 days of treatment with a standard dose of PPI and 50 mg of tegoprazan was 43.1 and 57.8 %, respectively [30]. Decreased proportion of patients with sleep disorders due to GERD-related symptoms was also observed with both PPIs and P-CABs. However, time to the first reported elimination of nocturnal heartburn with tegoprazan was 1.5 days, and with PPI it was 3 days. Thus, considering the comparable safety profile of PPIs and P-CABs, in patients with nocturnal heartburn, tegoprazan may be the treatment of choice for achieving a faster and long-lasting clinical effect and improving sleep quality.

S. Han et al. have studied tegoprazan efficacy for nocturnal acid breakthrough [23]. At tegoprazan 50 to 200 mg administration in the evening, mean intragastric pH of ≥ 4 was achieved within two hours, while in subjects taking PPIs, a similar effect was achieved within 7 hours. In this study, a dose-dependent increase in the time with gastric pH > 4 was also observed: 58.55 % with tegoprazan 50 mg, 70.07 % with 100 mg, and 81.73 % with 200 mg. Thus, tegoprazan has demonstrated a rapid acid-suppressing effect, together with the long-term maintenance of gastric pH > 4 for the first 12 hours after drug administration.

In another study conducted by E. Yang et al., a single 50 mg dose of tegoprazan at bedtime resulted in rapid and pronounced inhibition of hydrochloric acid secretion [26]. Percentage of time with gastric pH ≥ 4 during the night, measured by daily pH-metry, was 66 %, compared to 36.1 % for PPIs. Mean intragastric pH level in subjects treated with P-CABs was 4.6 ± 0.7 for the entire time of night measurement.

Tegoprazan clinical efficacy and safety in patients with non-erosive reflux disease was evaluated in a prospective, randomized, double-blind, placebo-controlled study by S.H. Kim et al. [31]. 324 patients with non-erosive GERD were allocated into three groups: Group 1 received tegoprazan 50 mg, Group 2 — tegoprazan 100 mg

and Group 3 — placebo, during one month. The symptoms (frequency and severity of heartburn, belching, dyspeptic complaints) were evaluated using the Reflux Disease Questionnaire (RDQ) before treatment and after 2, 4 and 6 weeks of therapy. In the fourth week, complete elimination of symptoms was observed in 42.5 % of patients treated with tegoprazan 50 mg, in 48.9 % treated with tegoprazan 100 mg, and in 24.2 % of patients received placebo ($p = 0.0058$, $p = 0.0004$, respectively, compared to placebo). Thus, this P-CAB was significantly superior to placebo in eliminating the major symptoms in patients with non-erosive GERD.

In 2024, a meta-analysis of 12 RCTs evaluating the P-CABs and PPIs efficacy and safety in the treatment of acid-related disorders was published [32]. In patients with erosive esophagitis, erosion healing rates associated with use of tegoprazan 50 and 100 mg/day were 72.1 and 58.3 %, respectively, compared to 40.7 and 28.9 % with fexuprazan 40 mg/day or esomeprazole 40 mg/day, respectively.

S. Seo et al. compared the efficacy of P-CAB with PPI in various GERD phenotypes [33]. The authors have noted that in patients with erosive esophagitis, especially severe, the use of P-CABs resulted in a faster therapeutic effect during initial and maintenance therapy. This group of medicines may be considered as an effective alternative to PPIs in the treatment of non-erosive GERD and PPI-resistant GERD.

A systematic review and meta-analysis of 4 RCTs ($n = 1834$) by Q. Zhuang et al. have shown that maintenance P-CAB therapy in patients with severe erosive esophagitis (Grades C and D according to the Los Angeles classification) was more effective compared to other antisecretory agents [34].

A systematic review and meta-analysis of 14 RCTs (4868 patients) have shown that P-CABs was not inferior to PPIs [35]. Odds ratio (OR) for erosive esophagitis healing frequency at weeks 2, 4, and 8 with P-CAB compared to PPI/placebo was 2.10 (95% CI: 1.53–2.88), 1.09 (1.05–1.14), 1.03 (1.00–1.06), and 1.03 (0.99–1.06), respectively. Of note, overall odds ratio (OR) for adverse events at P-CAB treatment compared to PPI/placebo was 1.08 (95% CI: 0.88–1.12). The results of this meta-analysis demonstrate high efficacy of P-CAB, comparable to that of PPI, together with similar safety profile.

In a multicenter, randomized, double-blind, comparative study, K.J. Lee et al. studied tegoprazan and esomeprazole efficacy and safety in patients with erosive esophagitis [36]. 300 patients (181 men, 119 women, aged 20–75 years) with endoscopically confirmed erosive esophagitis Grades A–D according to the Los Angeles classification were divided into three groups: Group 1 received tegoprazan 50 mg/day, Group 2 — tegoprazan 100 mg/day, and Group 3 — esomeprazole 40 mg/day. The primary endpoint of the study was the proportion of patients with esophagus erosions healing after 8 weeks of therapy. The cumulative rate of esophagitis healing was 98.9 %, 98.9 % and 98.9 % for tegoprazan 50 mg/day, 100 mg/day, and esomeprazole 40 mg/day, respectively. The authors have reported comparable efficacy, together with safety and good tolerability, for all three regimens.

Another multicenter, randomized, double-blind, parallel, controlled phase III study was conducted to evaluate tegoprazan efficacy in patients with erosive esophagitis [37]. 248 patients were divided into two groups: tegoprazan 50 mg/day group and esomeprazole 40 mg/day group. After 4 weeks of therapy, the frequency of esophagitis healing based on endoscopy data, changes in Reflux Disease Questionnaire (RDQ) and GERD-HRQL scores, and symptom improvement were assessed. The cumulative index of erosion epithelialization after two months from treatment initiation was also compared. According to RDQ, both groups have shown a comparable decrease in the disease symptoms intensity and frequency, and a comparable improvement in quality of life of patients (according to GERD-HRQL). The frequency of adverse events associated with PPIs and P-CAB was also similar, which further emphasizes similar safety and good tolerability of these drug groups. The cumulative erosion healing index according to endoscopic examination after 8 weeks of treatment was 91.1 and 92.8 % in the tegoprazan and esomeprazole groups, respectively. This study further confirms non-inferiority of tegoprazan compared to esomeprazole in terms of efficacy and safety in treatment of patients with erosive esophagitis.

In a double-blind, multicenter, phase III trial Y.K. Cho et al. studied the efficacy of maintenance therapy with tegoprazan in patients with endoscopically confirmed healed erosive esophagitis [38]. All patients were divided into two groups: Group 1 received tegoprazan 25 mg, Group 2 — lansoprazole 15 mg/day for 6 months. The study purposes included assessment of endoscopic remission frequency after 12 and 24 weeks, evaluation of adverse events, clinical laboratory investigations, and gastrin and pepsinogen I/II

serum levels. At tegoprazan treatment, endoscopic remission frequency after 6 months was 90.6 %, which was comparable to lansoprazole (89.5 %), regardless of the erosive esophagitis grade ($p = 0.47$). Baseline serum gastrin level in patients from tegoprazan group before the maintenance therapy initiation was 91.27 pg/mL, in lansoprazole group — 102.20 pg/mL. After 4, 8 and 24 weeks, gastrin and pepsinogen I/II levels were lower compared to baseline levels in the tegoprazan group.

Another multicenter, randomized, double-blind comparative study enrolling 218 patients with endoscopically confirmed erosive esophagitis (Grades A–D according to the Los Angeles classification) has shown the advantages of tegoprazan [39]. One group of study subjects received tegoprazan 50 mg/day, the other — lansoprazole 30 mg. CYP2C19 genotypes of the respondents were studied, drug tolerability was assessed, and the safety profile of the drug products was compared. After 14 days of therapy, the cumulative rate of the esophagus erosions healing was 88.4 % (91/103) and 82.6 % (90/109) (95% CI: 5.78 [–3.66–15.22], $p = 0.0005$) in the first and second groups, respectively. By week 4, the proportion of patients with healed erosive esophagitis according to esophagogastroduodenoscopy in tegoprazan group was 95.2 % (98/103), and in lansoprazole group — 86.2 % (94/109) (95% CI: 8.91 [1.22–16.59], $p < 0.0001$). The authors have shown tegoprazan superiority in relation to esophagus erosion healing, regardless of CYP2C19 genetic polymorphism. A significant relief of disease symptoms was also observed. The major GERD symptom, heartburn, was evaluated daily for two weeks. No statistically significant difference was reported between the tegoprazan and lansoprazole groups regarding proportion of patients without heartburn and proportion of days without heartburn. Comparable clinical efficacy and tolerability of the drug products studied have been shown.

A meta-analysis of 34 studies (25,054 patients) was conducted by Y. Liu et al. to compare the efficacy of various PPIs, P-CABs, and placebo in terms of the erosive esophagitis healing [40]. Among all patients included in the analysis, severe erosive esophagitis was observed in approximately 10 % cases. It was shown that the use of most P-CABs resulted in higher esophagus erosion healing rate compared to PPIs, especially in patients with severe erosive esophagitis. The rate of erosions healing with tegoprazan 50 or 100 mg/day was higher compared to that with PPI (ilaprazole, esomeprazole, pantoprazole, lansoprazole, omeprazole, rabeprazole) in standard or double doses, both at weeks 4 and 8. It should be noted that for most treatment regimens, the cumulative rate of erosion healing after 8 weeks of therapy was significantly higher than the rate after 4 weeks.

Position of tegoprazan in modern clinical guidelines for GERD diagnostics and treatment

In the guidelines for GERD diagnostics and treatment of Russian Gastroenterological Association (2024), P-CABs are considered as promising antisecretory agents for the treatment of acid-related disorders in the future [4].

In the GERD guidelines of Japanese Society of Gastroenterology (2021), the use of P-CABs (vonoprazan) is recommended as initial/maintenance therapy in severe reflux esophagitis [41], and in mild reflux esophagitis use PPIs or P-CABs is proposed.

In the Seoul Consensus on the GERD diagnostics and treatment (2021), P-CABs have been recommended as initial treatment for GERD and erosive esophagitis [42]. It has been emphasized that this drug class is not inferior to PPIs in terms of efficacy.

The guidelines on GERD management of the Asia-Pacific Consensus (2021) also outline the advantages of using P-CABs in GERD, especially in severe erosive esophagitis [43].

Conclusion

Tegoprazan belongs to a new class of potassium-competitive blockers of hydrochloric acid secretion, and according to clinical study data, it possesses several advantages in the treatment of acid-related disorders. P-CABs are not prodrugs, which results in faster and longer-lasting antisecretory effect that does not depend on food intake. Tegoprazan mechanism of action is not affected by CYP2C19 genetic polymorphisms, and there is no risk of drug interactions. These factors determine the advantage of P-CABs in patients with nocturnal heartburn, nocturnal acid breakthroughs, non-erosive GERD, erosive esophagitis.

The results of previous studies demonstrate high potential of this class of drugs in the treatment of acid-related disorders. However, further studies to confirm long-term efficacy and safety data are required, including that in the Russian Federation.

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