ANTISECRETORY ACTIVITY OF ESOMEPRAZOLE (EMANERA) IN THE CONDITIONS OF LONGTERM MONITORING OF INTRAGASTRIC PH IN PATIENTS WITH ACID-RELATED DISEASES

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Aim of the study: The research of antisecretory potential of generic medicine esomeprazole - Emanera (KRKA).

Subjects and methods: Long-term (48-hour) monitoring of intragastric pH was performed in 10 patients with acid-related diseases (ulcer disease and erosive gastroduodenitis) using 'Gastroscan-24' (Istok-Sistema, Fryasino). All patients received a 40 mg dose of the medicine Emanera on the second day of the study. In the study the following parameters were estimated: the mean and median daily pH values; the median time of maintenance of pH >4 and >6; the proportion of time with the corresponding pH values; the area under the pH distribution curve from 1 to 10. Corresponding parameters before and after the administration of 40 mg of Emanera were compared using the Wilcoxon test. The differences were considered significant at $p < 0.05$.

Results of the study: The study demonstrated high antisecretory potential of the medicine. After a short latent period (1.27 hours on average), a significant increase of pH in gastric corpus was obtained in response to the first dose (40 mg) of the medicine The median of mean daily pH values was 6.25. A comparison of the area under pH distribution curves (in 24 hours) before and after the administration of the medicine has confirmed an increased antisecretory activity of Emanera. Cases of intrinsic resistance were not observed.

Conclusion: Emanera® in a 40 mg dose can be used in acid-related conditions, including the conditions that require suppression of increased acid levels (optimisation of eradication therapy, erosive GERD and Barrett's esophagus, extraesophageal manifestations of GERD and others).

Acid-related conditions are very important in therapeutic practise. The need for gastric acid secretion blockade occurs in peptic ulcer and pre-ulcer conditions, symptomatic ulcers, gastroesophageal reflux disease, pancreatitis and others. (1). Gastric acid secretion inhibitors are the important component of the eradication of *Helicobacter Pylori*; the indications for eradication therapy are expanding and include not only acid-related diseases but also non-gastric manifestations of infections, such as unexplained iron deficiency anemia and idiopathic thrombocytopenia [2]. Therefore, the evaluation of the functioning of the stomach has been at the centre of attention of gastroenterologists for many years; evaluation methods have been improving from testing the extracted gastric juice to the short-term (1-3 hours) intragastric pH-metry (3, 4). The improvement of pH-metric probes and software enabled the conduction of long-term monitoring of inesophageal and intragastric pH values (5, 6, 7, 8).

A 24-hour gastric pH-metry evaluates acid formation processes within 24 hours under normal conditions which include food intake, smoking, horizontal or vertical position of the body or medicine administration, which distinguishes this method from the ones previously used (9, 10, 11). In addition, long-term pH monitoring also enables detection of resistance to a specific secretion inhibitor and of the nocturnal acid breakthrough, both of which require a special therapeutic approach. So the role of this study in diagnostics and differential diagnostics of GERD, especially in atypical and extraesophageal manifestations, is indispensable (12, 13).

Based on long-term pH monitoring the requirements for gastric acid secretion levels were set in different clinical situations. In 1990, the Canadian scholars (14), who were analysing 490 protocols of 24-hour gastric pH monitoring in different treatment regimens of ulcer diseases, established that for the optimal ulcer healing the values of gastric pH should be >3 for18 hours per day for 4 weeks. These authors also demonstrated that the treatment of erosive esophagitis requires more expressed suppression of acid secretion: the maintenance of pH in esophagus >4 for 21 hours and more within 8 weeks (15). After that, the American scientists demonstrated that better eradication effect of *H.Pylori* is achieved with mean daily pH > 6. It was established that *H.Pylori* survives, but it can turn into a non-replicative state (phenotypic resistance), when pH in their microenvironment is lower than 6 and higher than 3 (16). This occurs in the mucus layer and is demonstrated not only by a direct change of gene expression of *H.Pylori* (17), but also indirectly by improved efficacy of antibacterial therapy in removing the mucus layer using pronase (18). At pH value 6-7 *H.Pylori* actively replicates and becomes more sensitive to antibacterial medicines, including clarithromycin and amoxicillin (19). Requirements for gastric

acid secretion inhibition in gastric hemorrhage and extraesophageal manifestations of GERD are also very strict (maintenance of pH >6). At the same time, the requirements are not so demanding in functional dyspepsia, maintenance therapy of GERD and prophylaxis of NSAID-gastropathy. Therefore, in a specific clinical situation the secretion inhibitor can be chosen by a doctor. Selection of the right medicine can also be influenced by data on the actual antisecretory activity of a medicine, which can be determined by long-term pH monitoring. 24-hour pH monitoring also showed weaknesses of H2-inhibitors (insufficient antisecretory effect, presence of the 'fatigue syndrome of receptors' with a sharp decrease of antisecretory activity from the fifth day of administration of the medicine), which resulted in decreased use after the launch of proton pump inhibitors. Advantages of the first PPI (omeprazole) over H2-inhibitors were already demonstrated at the beginning of our 20-year experience with 24-hour pH monitoring. In the majority of generic omeprazoles the antisecretory response was significantly lower than in the reference (original) medicine (and with the large spread of parameters among individual brands), the predictability was even worse: the resistance level reached 20%, which was difficult to explain in terms of pharmacokinetic properties of omeprazole. As a result, the issue about the quality of several generic medicines was brought up (Table 4 (20, 21, 22)). At the same time, further studies of antisecretory activities of some generic lansoprazole and pantoprazole demonstrated their similarities with the effect of the original omeprazole (23, 24).

The development of esomeprazole brought several other advantages: levorotatory optical isomer of omeprazole with more advantages than dextrogyrate isomer and racemate of omeprazole in terms of several pharmacokinetic parameters. Slow clearance rates of esomeprazole enable longer persistence and intensity of the antisecretory effect. A smaller participation rate of CYP 2C19 isoenzyme in the metabolism of esomeprazole (in comparison to omeprazole) is also important as it is associated with a smaller formation of inactive metabolite and the creation of a higher concentration of a medicine in blood plasma, as well as with better predictability of antisecretory response (with lower dependence on metabolic rates associated with genetic CYP 2C19 polymorphism) and a better interaction profile with other medicines (25); these pharmacokinetic advantages of esomeprazole are used in clinical practise for a more rapid and reliable symptom relief and healing of erosions and ulcers etc. (26, 27).

Considering a different (not only intra-group, but also inter-group) antisecretory effect of original medicines and generic PPIs received earlier (22, 23), it seems advisable to evaluate the antisecretory potential of new generics that emerge on the Russian market.

Aim of the present study to evaluate the antisecretory efficacy of the first dose of esomeprazole - KRKA's Emanera in the long-term (48 hours) monitoring of intragastric pH.

The study included 10 patients with gastroduodenal pathology (gastric or duodenal ulcer, erosive gastritis) with an average age of 48±1.75 years that signed the informed consent to participate in the study. Patients did not receive secretion inhibitors for 3 days before the study and possible symptoms could be relieved with antacids. The study of intragastric acidity was performed with the instrument 'Gastrocscan-24' (the Istok-Sistema company, Fryazino) for 48 hours. Prior each testing the system was calibrated by standard buffer solutions of nominal value at 37± 1°C «1.2» and «9.18». The location of electrodes in cardinal, corpus and antral sections was controlled with X-ray. On the first day, patients with a normal lifestyle were not given any medicines and on the second day, they received 40 mg of Emanera 30 minutes before breakfast.

Standard parameters were evaluated during the 1st and 2nd day: mean daily values and median pH in gastric corpus and antral section of the stomach; mean maintenance time of pH >3 - >7 and a proportion of time (presented as a percentage of a day) with the corresponding values of pH (>3 - >7) in gastric corpus. In addition, medians of the area under pH distribution curves from 1 to 10 were evaluated (during the day) in corpus and antral part of the stomach (S unit/min).

The difference of tested parameters values before (on the first day) and after the administration of 40 mg of Emanera was estimated (Δ between the first and the second day). On the second day a latent period was estimated - time from the medicine administration to the increase of pH >4.

Statistical analysis of the results was performed in SPSS program, version 15. Considering the paucity of the group and irregularity of parameter distribution, non-parametric methods were used to calculate the significance of the differences between 1st- and 2nd-day parameters and Wilcoxon test was used to compare two dependent samples. The Parameter of significance of difference was $p<0.05$.

Baseline mean daily pH (on the first day) in the gastric corpus was 3.21±1.9 (at the value distribution from 1.53 to 5.27); in the antral section it was 5.17±1.78 (at the value distribution from 1.75-5.-24). After the administration of 40 mg of Emanera, the mean daily pH in the gastric corpus increased to 6.25 ±1.25 (at the variations from 4.02 to 7.92) and to 6.75±0.92 (at the

variations in values from 5.81-8.07) in the antral section. So, the secretion in the gastric corpus was suppressed by 48.6% (pHΔ = 3.05 ± 0.44), accordingly, the acidification of the antral section was reduced by 23.4% (pHΔ = 1.58 ± 0.44). Similar dynamics were demonstrated in the median of mean daily pH: median pH in the gastric corpus increased by 46.4%. (Table 1).

Table 1. Median of mean daily pH before and after the administration of 40 mg of Emanera.

Parameter	Before the administration of Emanera (first day)		After the administration of 40 mg of Emanera (second day)		The increase of median pH (in %) for gastric corpus
	corpus	antrum	corpus	antrum	
median pH	2.90	5.42	6.25**	6.73*	46.4%
Spread of values 25 - 75	2.11 - 4.41	4.14 - 6.37	5.80 - 7.00	6.29 - 7.10	

** - the significance of differences in median pH in gastric corpus before and after the administration of Emanera ($p<0.005$); * - the significance of differences in median pH in antral section ($p<0.013$). The evaluation was performed by Wilcoxon test ($p<0.013$)

Both methods of evaluation of mean daily pH parameters (mean and median) have demonstrated very close values of pH increase not only in the corpus, but also in the antral section of the stomach showing a considerable reduction of stomach acidity, i.e. good antisecretory properties of the medicine Emanera. Figure 1 demonstrates a significant increase in intragastric pH parameters on the second day of the study (after the administration of 40 mg of Emanera) with 48-hour monitoring of patients with erosive gastroduodenitis (corpus electrode).

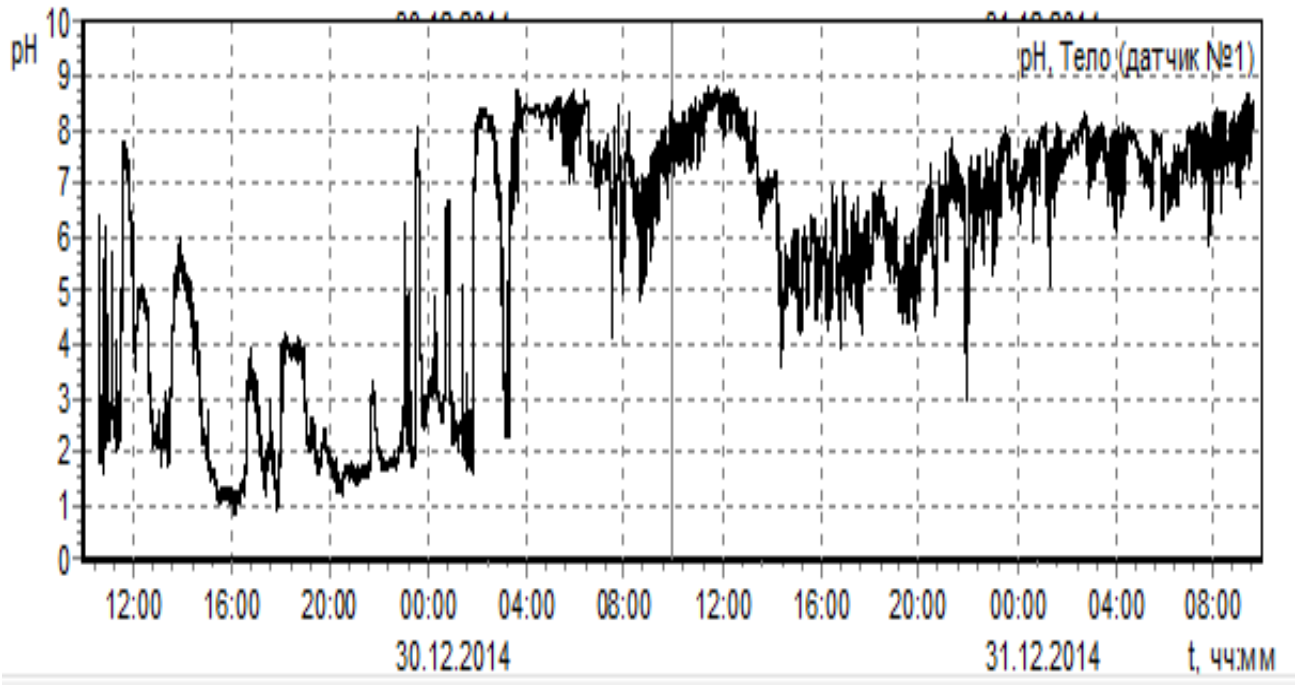

Fig. 1. Patient G-va 48-hour pH-gramm (gastric corpus) On the first day (without medications): time with pH < 1.6 = 9.9 hour; mean daily pH values = 4.3; the percentage of time with pH > 4 = 43.9%; latent period = 28 min.; mean daily pH = 7; time with pH < 1.6 = 0; time with pH > 4 = 12.3 hour; the percentage of time with pH > 4 = 99.7%

For an additional demonstration of antisecretory properties of the medicine Emanera, the calculation of the mean maintenance time of different pH values (according to the requirements for different clinical situations) and the percentage of time with the corresponding pH values in a day was performed. After the administration of 40 mg of Emanera a highly significant increase in the percentage of time with all pH values was observed: triple - with pH > 4, four-times - with pH >5, five-times - with pH >6. Even the time with pH >7 was increased by 4.5 times (Table 2). Consequently, the percentage of time (in a day) with the corresponding pH values also significantly increased reaching more than 85% at pH >4 and more than 60% at pH >6 (Table 3).

Table 2. Mean proportion of time with different pH values before and after the first dose of Emanera (esomeprazole), corpus electrode

Study period	Time with pH >3, min (h)	Time with pH >4, min (h)	Time with pH >5, min (h)	Time with pH >6, min (h)	Time with pH >7, min (h)
Without PPI (1st day)	503±97.1 (8.4± 1.62)	349±78.2 (5.9± 1.31)	237±56.2 (3.9± 0.94)	155.9±46.7 (2.6± 0.78)	105.7±40.7 (1.7± 0.68)
2nd day (40 mg of esomeprazole)	1159±87.9 (19.0± 1.36)	1109±94.7 (18.5± 1.58)	1000±108.8 (16.7± 1.81)	787±113.3 (13.1± 1.89)	465±121.3 (7.8±2.0)
P	<0.005	<0.005	<0.007	<0.005	<0.007
Δ pH 1st - 2nd day	656±94.4 (10.9 ±1.58)	758±85.5 (12.6± 1.42)	753±88.3 (12.7± 1.44)	633±88.3 (10.54± 1.47)	361±103.7 (6.04± 1.74))

Table 3. Percentage of time with different pH values before and after the first dose of Emanera (esomeprazole), (corpus electrode)

Study period	% of time with pH>3	% of time with pH>4	% of time with pH>5	% of time with pH>6	% of time with pH>7
1st day (without PPI)	43.4±8.76%	31.4±8.07%	24.1±5.31%	12.6±3.40	8.7±3.08%
2nd day (40 mg of esomeprazole)	89.2±4.65%	85.2±5.19%	72.6±8.83%	60.1±6.99%	31.3±8.7%
p	<0.007	<0.005	<0.009	<0.005	<0.017
Δ	45.8±7.97%	53.7±6.71%	55.4±5.33%	46.5±5.33%	22.6±7.67%

Such a large antisecretory reaction was not observed for any of (generic) omeprazole in our previous studies (24-hour pH-metry) (Table 4).

Table 4. Duration of antisecretory reaction in hours and percentage of maintenance time for different pH values for generic omeprazole

Product	n	pH > 3 hour / %	pH > 4 hour / %	pH > 5 hour / %	pH > 7
OME* 20 mg	12	3.7 ± 3.33 15.1 ± 13.77	2.6 ± 2.44 11.0 ± 10.23	2.0 ± 1.83 8.3 ± 7.64	-
OME* 40 mg	18	11.7 ± 0.10 46.7 ± 4.47	9.7 ± 0.81 40.3 ± 3.38	8.3 ± 1.04 34.6 ± 4.32	-
OME** 20 mg	10	6.0 ± 4.18 27.5 ± 19.26	4.6 ± 3.16 19.1 ± 13.18	3.9 ± 2.72 16.4 ± 11.39	-
OME*** 20 mg	10	3.5 ± 3.77 14.6 ± 15.71	2.5 ± 2.62 10.3 ± 10.92	2.0 ± 2.08 8.2 ± 8.66	-
OME**** 20 mg	17	6.3 ± 4.29 26.3 ± 17.89	4.7 ± 3.17 19.7 ± 13.21	3.9 ± 2.61 16.1 ± 10.88	-
OME***** 20 mg	10	10.3 ±1.20 30.2±13.75	6.4+2.90 26.8±12.80	5.3+2.60 22.0+10.83	-

Note: Asterix denotes omeprazole generics of different producers.

Latent time for 40 mg of Emanera was 1.27 hours, so the bioavailability was not different from the latent period obtained earlier for the original esomeprazole (23). In fact, areas under the curve of plasma concentration of medicines Nexium and Emanera did not differ when investigating bioequivalence of generic medicine in relation to the original medicine. It has therefore been confirmed that the formulation of esomeprazole by Krka, produced in capsules, is bioequivalent to the formulation of reference tablets of esomeprazole (28).

Median area under the pH distribution curve from 1 to 10 (in 24 hours of the study) in gastric corpus after the administration of 40 mg of Emanera was 6800 unit/min vs 3915 unit/min on the first day of the study before the administration of the medicine, i.e. it increased by more than 40%. (Fig. 2) The same increase of this parameter was observed also in the antral section (from 2510.4 unit/min to 3359.4 unit/min, i.e. by almost 39%), Fig. 3.

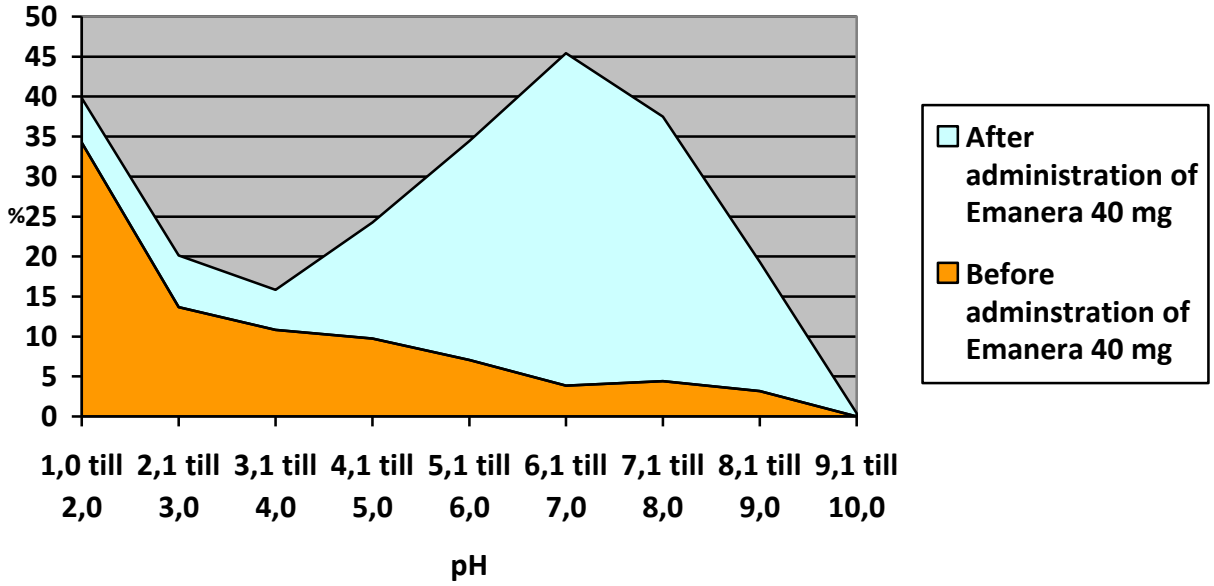

Fig. 2. Graph of pH distribution from 1 to 10 (in a day) before and after the administration of Emanera 40 mg (in gastric corpus)

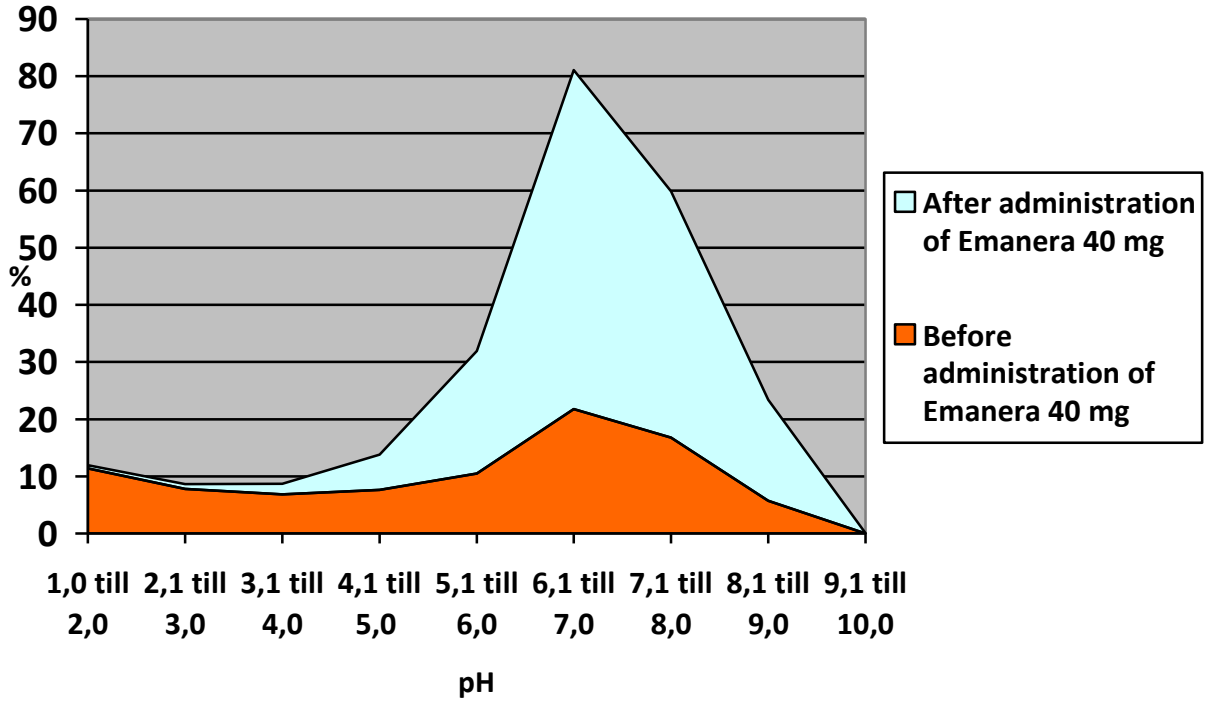

Fig. 3. Graph of pH distribution from 1 to 10 (in a day) before and after the administration of 40 mg of Emanera (in antral section of the stomach)

Considering the fact that the repeated administration of PPI causes increased antisecretory activity (19), the protracted treatment can lead to even higher antisecretory activity of the tested medicine.

High antisecretory activity of the medicine Emanera is definitely provided by the gastro-protected pharmaceutical form: in this form esomeprazole is contained in acid-resistant pellets that are released from the capsule in the stomach - this protects the stomach against the acid gastric content and provides better bioavailability in the release of the pellets in the intestinal tract. In addition, such form is convenient for people with swallowing difficulties and on occasions when it is necessary that the medicine is administered through the probe (capsules Emanera can be opened and pellets can be taken with non-sparkling (negazirano) water or administered with water through the probe). The credibility of the medicine Emanera© is also assured by Krka's own process of synthesis of a substance and pellets, the formulations of which are patent-protected. The medicine is produced in accordance with all GMP requirements. This is also proven by several documents issued by European regulatory authorities.

Long-term (48-hour) monitoring of intragastric pH has demonstrated high antisecretory reaction of Emanera in a 40 mg dose already at the first administration. There were no cases of refractoriness with the administration of 40 mg, the dispersion of inter-individual values was not high, which resulted in good predictability of antisecretory reaction.

After the first administration of Emanera in a 40 mg dose, mean maintenance time of pH > 4 was approx. 18 hours, mean percentage of time with such pH was approx. 80% of a day; mean maintenance time of pH > 6 was approx. 13 hours (with median line - 15 hours), while the mean percentage of time with such pH was approx. 60% of a day.

Mean daily pH value after the first administration of 40 mg of Emanera was impressive (more than 6) and in addition, they were the same when median and mean were calculated. Median of area under the distribution curve of pH values from 1 to 10 after the administration of 40 mg of Emanera increased by 46.4% which most vividly demonstrates the antisecretory efficacy of the medicine.

High antisecretory activity of Emanera in a 40 mg dose, absence of refractoriness and good predictability allows recommendation of the use of the medicine in the treatment of acid-related diseases, including situations with high demands to PPI (optimised eradicational

therapy, erosive GERD, Barrett's esophagus, extraesophageal manifestations of GERD and others).

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