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ANALYSIS OF CURRENT DATA ON THE SAFETY AND EFFICACY OF THE PHLOROGLUCINOL AND SIMETICONE COMBINATION (LITERATURE REVIEW)

Actuality. *The article, based on studies of literary sources, provides data on the use of a combination of the herbal medicinal product of spasmolytic action phloroglucinol with the absorbent simethicone for the treatment of functional disorders of the digestive tract. Phloroglucinol has an antispasmodic effect, as a selective blocker of calcium channels, which suppresses spasm of smooth muscles while maintaining peristalsis. Simethicone absorbs foam and gases, reducing flatulence, discomfort and pain in the gastrointestinal tract. The drug of plant origin with a surface-active substance is a low-toxic compound effective for the therapy of functional disorders of the alimentary canal.*

The purpose of the work. Analysis and generalization of experimental and clinical data on the safety and effectiveness of the combination of simethicone and phloroglucinol.

Material and methods. *An analysis of literary data from domestic and foreign literature was carried out to assess the clinical effectiveness and safety of using a combination of a herbal preparation with antispasmodic action of phloroglucinol with the absorbent simethicone. To assess clinical efficacy and safety, the authors used a literature review based on PubMed, MEDLINE, Web of Science, and Scopus databases.*

Research results. *The effectiveness and safety of the combined mechanism of action of phloroglucinol and simethicone for the treatment of functional disorders of the digestive tract is shown.*

Conclusion. *The drug based on phloroglucinol and simethicone is an effective and safe therapeutic agent for the additional treatment of functional disorders of the alimentary canal.*

Key words: *phloroglucinol, simethicone, digestive tract, intestinal disorders, evidence-based medicine.*

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АНАЛІЗ СУЧАСНИХ ДАНИХ ЩОДО БЕЗПЕКИ Й ЕФЕКТИВНОСТІ КОМБІНАЦІЇ ФЛОРОГЛЮЦИНОЛУ ТА СИМЕТИКОНУ (ОГЛЯД ЛІТЕРАТУРИ)

Актуальність. *У статті на основі досліджень літературних джерел наведено дані щодо застосування комбінації лікарського засобу рослинного походження спазмолітичної дії флороглюцинолу з абсорбентам симетиконом для лікування функ-*

ціональних розладів травного каналу. Флороглюцинол виявляє спазмолітичний ефект як селективний блокатор кальцієвих каналів, який пригнічує спазм гладеньких м'язів при збережені перистальтики. Симетикон абсорбує піну й гази, зменшуючи метеоризм, дискомфорт і біль у шлунково-кишковому тракті. Препарат рослинного походження з поверхнево активною речовиною є малотоксичною сполукою, ефективною для терапії функціональних розладів травного каналу.

***Мета дослідження** – аналіз та узагальнення експериментальних і клінічних даних щодо безпеки й ефективності комбінації препарату симетикону та флороглюцинолу.*

***Матеріал і методи.** Проаналізовано літературні дані вітчизняної та зарубіжної літератури для оцінювання клінічної ефективності й безпечності використання комбінації препарату рослинного походження з спазмолітичною дією флороглюцинолу з абсорбентам симетиконом. Для оцінювання клінічної ефективності та безпеки автори використали огляд літератури на основі баз даних PubMed, MEDLINE, Web of Science і Scopus.*

***Результати дослідження.** Показана ефективність і безпека комбінованого механізму дії флороглюцинолу та симетикону для лікування функціональних розладів травного каналу.*

***Висновок.** Препарат на основі флороглюцинолу та симетикону є ефективним і безпечним терапевтичним засобом для додаткового лікування функціональних розладів травного каналу.*

***Ключові слова:** флороглюцинол, симетикон, травний канал, кишкові розлади, доказова медицина.*

Introduction. Functional intestinal disorders are some of the most common diseases, registered by primary care doctors and specialized gastroenterological clinics. Notwithstanding their benign character, these diseases substantially affect health-related quality of life. At present, among therapeutic options for functional intestinal disorders medical therapy prevails and the treatment, as a rule, is aimed at the relief of dominating symptoms (Aboubakr & Cohen, 2021).

As it is recognized that the changed motility underlies the majority of intestinal disorders, spasmolytics remain a mainstay for pharmacological treatment. Spasmolytic agent phloroglucinol has been used for decades and has proven its efficiency for the relief of these symptoms in several clinical trials. It is often prescribed in combination with intestinal absorbents, such as simethicone (Ben Ner et al., 2023; Koshurba et al., 2023).

The medicinal products based on this combination have been present already for a long time in the global pharmaceutical market. The first combination of simeticone and phloroglucinol dihydrate was registered in 1996 in France, that is, more than 25 years ago, as additional remedy for treatment of functional intestinal symptoms, in particular, meteorism and diarrhea. At present time, this product is still marketed in the EU countries. In Ukraine, this product has been marketed since 2011 (Tkach, 2020).

Phloroglucinol is a secondary metabolite of natural (plant) origin. In nature, it is found in some types of plants, it is also produced by brown algae and bacteria. It is a part of flavones and catechins in the form of glycosides, in particular, it is part of flavone and anthocyanin pigments, giving color to colors. The name of the substance is due to its distribution in plants (fluoro-) and sweet taste (-glucin) (Bai et al., 2024; Blanchard et al., 2018).

Pharmacologically, phloroglucinol dihydrate is a nonatropine antispasmodic, a selective blocker of calcium channels, which prevents the development of spasm of smooth muscle cells without causing atony or hypotonia of the intestines. Unlike non-selective antispasmodics, phloroglucinol has no systemic side effects (Jung et al., 2021). One of the mechanisms of action of phloroglucinol is its inhibitory effect on the process of lipid peroxidation, which reduces inflammation. As a result of the complex combined mechanism of action of phloroglucinol, an antispasmodic effect is realized at the level of the body: spasms of smooth muscles are suppressed with preserved peristaltic activity.

Simethicone is an inert, non-toxic surfactant with an antifoaming action that reduces abdominal distension, discomfort, and pain. It acts on the surface of air bubbles, reducing their surface tension and contributing to their dispersion. Simethicone can act as a topical mucosal barrier, providing protection against irritants such as stomach acid, bile salts and bloating (Beaufort et al., 2023; Meier et al., 2007).

Simethicone is not absorbed by the mucous membrane of the gastrointestinal tract; it is chemically inert, non-toxic and does not cause side effects. By adding simethicone to antispasmodics in the treatment of irritable bowel syndrome, general symptoms and bloating are reduced (Martínez-Vazquez et al., 2012).

The phloroglucinol and simeticone combination has been used for a long time in a number of pathologies of the gastrointestinal tract, therefore it is important to analyze the effectiveness and safety of the combination from the point of view of evidence-based medicine, which involves improving the results of patient treatment by facilitating informed decision-making, optimizing the choice of treatment and reducing the use potentially ineffective interventions (Galkin et al., 2018; Ratnani et al., 2023). The highest level of evidence is considered to be a systematic review and meta-analysis of relevant medical technologies (Grigorieva et al., 2019; Ratnani et al., 2023; Shesterenko et al., 2023).

The purpose of the work is to analyze and generalize actual data on the safety and effectiveness of the combination of drugs simethicone and phloroglucinol.

Reports on studies of safety and efficiency of simeticone. Simeticone is physiologically inert mixture of completely methylated linear siloxane polymers, stabilized by silicon dioxide. As such, it does not have pharmacological properties and usually is used as an excipient (Goodman & Gilman's, 2020). It has physical antifoaming properties and is used as an agent against meteorism. It decreases liquid surface tension, thus causing the merging of gas bubbles in intestine and promoting their dispersion. Simeticone is also used as antifoaming agent in radiology and gastrointestinal endoscopy (Martindale, 2005).

Simeticone is a non-toxic surface-active agent, based on silicone, a foam suppressant. It eliminates air bubbles in meteorism by changing their surface tension. The evolving gas is absorbed and/or eliminated in natural way. Simeticone acts exclusively on the gas bubble surface and is not absorbed by mucous membrane of gastrointestinal tract.

Simeticon is the most well-known and safe antiflatulent, used for almost fifty years for symptomatic treatment of meteorism and as premedication before radiological, endoscopic, and sonographic examinations of gastrointestinal tract (Rémy et al., 2007). It increases liquid surface tension and destroys small gaseous bubbles in foam, causing antifoaming and antiflatulent effects. Simeticone is not absorbed; it is chemically inert, nontoxic, and does not cause adverse effects. This substance is non-toxic, with efficiency and safety proved by numerous studies.

Simeticone products are available in the EU and are indicated for pediatric use for symptomatic relief of dyspepsia, heartburn, meteorism, pressing pain, and infant colics. The majority of simethicone products, available in the UK, are indicated for children older than 12 years, only one product in the form of peroral suspension (40 mg/ml) is indicated for infants (age is not specified). Dosing for infants is 20–40 mg (0.5–1.0 ml) before each feeding. In the UK simethicone forms are available as one tablet and two capsules with dosing of 100–125 mg, indicated for children older than 12 years three-four times daily. According to the information from the pharmacovigilance database from the period from 01.07.1963 till 14.07.2016, 29 spontaneous reports of suspected adverse events were registered, associated with simethicone-containing products, used orally by children, however, no new safety data were revealed that would necessitate regulatory actions (Simeticone, 2006).

The double-blind placebo-controlled study of simethicone efficiency and tolerability in the therapy of postsurgical meteorism was performed in patients after the Caesarian section. Its results have demonstrated significant decrease in analyzed subjective complaints (nausea, vomiting, meteporism, abdominal discomfort, and abdominal pain) compared to placebo. In patients, who received simeticone, peristaltic movements developed in 100% of cases during the first days in the simeticone group, and only in 30% in placebo group. Meteorism also developed in all patients from simeticone group, compared to 20% in placebo group. Based on the obtained results, considering the product's non-toxicity, its chemically inert properties, food tolerability, and simplicity of use, the authors consider simethicone very useful for the prevention and treatment of post-surgical discomfort due to gas accumulation and gastrointestinal tract distension after Caesarian section (Avramović et al., 1979).

In the monitoring study by Michigan Medicaid Recipients, covering completed pregnancies in the period between 1985 and 1992, the authors registered 248 newborns, exposed to simeticone in the I trimester. They revealed 14 (5.6%) large birth defects against 11 expected. The specific data, available for 6 categories of birth defects (registered/expected), are the following: cardiovascular system – 6/2; polydactyly – 2/1; spina bifida – 0/0; orofacial cleft – 0/0.5; reduction limb defect – 0/0.5; hypospadia – 1/0.5. Only the cases of cardiovascular birth defects allow for possible association. However, other factors, such as maternal diseases, use of other products, and eventuality affected the cases with stronger probability, as simeticone is not absorbed.

Simeticone is prescribed, as a part of antacid therapy before the Caesarian section. No associated adverse effects in newborns are reported.

One placebo-controlled study examined simeticone efficiency in diagnostic tests of intestine. This study included 86 patients, who received either simeticone (n=42), or placebo (n=44) in addition to peroral sodium phosphate to determine if simeticone improved visualization during colonoscopy. Five zones of the large intestine (rectosigmoid colon, descending colon, transverse colon, ascending colon, and caecum) were assessed for the presence of air bubbles after endoscope removal. Thirteen patients in placebo group and only one patient in the simeticone group had a significant number of air bubbles. In addition, the average number of bubbles was higher in placebo group in each zone of transverse colon. This study shows that the use of simeticone together with sodium phosphate may improve visibility in the large intestine, decreasing the presence of bubbles. Such improved visualization may promote the detection of pathological lesions on intestinal mucous membranes (Sudduth et al., 1995).

One double-blind placebo-controlled study examined simeticone efficiency in treatment of functional gastroin-

testinal disorders. In total, 41 subjects participated in the study, randomized into two groups, with simeticone or placebo. The treatment course was ten days. The simeticone group demonstrated significant decrease in symptoms of functional gastrointestinal disorders: meteorism (P<0.001), sensation of heaviness (P<0.001), flatulence (P<0.005), distension (P<0.03), and stomach disorders (P<0.02) compared to placebo. Additionally, global rating showed significant clinical efficiency in patients with simeticone compared to placebo. The authors concluded that simeticone was a safe and efficient agent for decrease of symptoms of functional gastrointestinal disorders (Bernstein et al., 1974).

Capsule endoscopy is a new method of visualization of the entire small intestine. Capsule endoscopy was performed on 36 patients, who fasted for 24 hours before peroral administration of capsule. Before capsule endoscopy, 18 patients received simeticone 80 mg, and 18 patients did not receive additional agents for intestine preparation (Albert et al., 2004). During endoscopy, the authors assessed the visibility of the mucous membrane and the presence of intraluminal gas bubbles. It was demonstrated that simeticone promoted much better visibility with a lesser number of intraluminal bubbles (p<0.01), the visibility was excellent. No adverse effects of simeticone were observed. The authors concluded that simeticone may be added to routine preparation for capsule endoscopy for improvement of visibility of small intestinal mucous membranes (Albert et al., 2004; Ge et al., 2006).

The systemic review and meta-analysis of randomized controlled studies of simeticone use in endoscopy were carried out. The authors examined the effect of this agent on the following endpoints: quality of small intestine visualization, speed of performance, passage time through stomach, passage time through small intestine, diagnostic efficiency, intestine preparation efficiency, the number of air bubbles, and the duration of the procedure. In total, 13 studies were suitable for this meta-analysis; 4 studies were detected that compared laxatives or fasting plus simeticone and laxatives or only fasting for capsule endoscopy. For the patients, who additionally received simeticone before capsule endoscopy, the quality of small intestine visualization was significantly better ([Odds Ratio] OR=2.84, 95% Confidence Interval: 1.74–4.65, p=0.00), while the percentage of completion was comparable (OR=0.80, 95% CI: 0.44–1.44, p=0.454). Also, 7 studies were identified that compared laxatives plus simeticone with only laxatives for colonoscopy. For the patients, who received additional simeticone before colonoscopy, the effectiveness of large intestine preparation was comparable (OR=2.06, 95% CI: 0.56–7.53, p=0.27), however, the number of air bubbles decreased significantly (OR=39.32, 95% CI: 11.38–135.86, p=0.00). According to the results of the performed studies the authors concluded that the additional use of simeticone before endoscopy improved the visualization quality of the small intestine, especially in patients without laxatives, however, it did not affect the speed of completion of capsule endoscopy and decreased the air bubbles in large intestine lumen (Wu et al., 2010).

In the study of Gibstein A. et al., the results and statistical data are presented of the double-blind clinical trial in the period from July 1, 1964, till December 31, 1968, including 400 woman-patients, from whom 265 patients received simeticone and 135 did not receive simeticone. The product was used, in addition to the usual post-surgical procedure. It was shown that simeticone use by patients after gynecological and obstetrical procedures decreased gastrointestinal discomfort (Gibstein et al., 1971).

Simeticone is widely used in clinical practice, as anti-foaming agent. By decreasing surface tension of bubbles in the gastrointestinal lumen a bubble may be removed and image quality may be enhanced. In addition, this may lessen abdominal flatulence, which causes significant decrease in the number of patients with gastrointestinal discomfort symptoms. The study was performed, aimed at assessment of simeticone effects during intestine preparation for colonoscopy. This meta-analysis included eighteen randomized controlled studies in 7187 patients. Polyethylene glycol with simeticone improved purgation of the large intestine (P<0.00001), polyps (P=0.006), and the speed of lesion detection in the right colon (P<0.00001) compared to polyethylene glycol alone. There were no differences in adenomas (P=0.68), time of elimination (P=0.06), the rate of caecum intubation (P=0.98), and the time of caecum intubation (P=0.65) between the 2 groups. The rate of abdominal flatulence was higher in the polyethylene glycol group, however, there were no significant differences in vomiting (P=0.65) and abdominal pain (P=0.25). The authors concluded that simeticone improved the quality of purgation of the intestine, but not adenoma. Besides, simeticone improved the speed of detection of lesions in the right colon and decreased abdominal distension, however, it did not affect vomiting, pain, and abdominal spasms (Liu et al., 2021; Moolla et al., 2019).

The researchers conducted a randomized, placebo-controlled, double-blind clinical trial, aiming at the assessment of simeticone efficiency during preparation for esophagogastroduodenoscopy. The candidates for scheduled esophagogastroduodenoscopy received a simeticone chewing tablet 40 mg (n=90) or placebo (n=83) with 3 ml of water, 15–30 min. before esophagogastrodu-

odenoscopy. Air/foam bubbles during the endoscopy were assessed by 4-point scale, and patient satisfaction with endoscopy was assessed from 0 to 10 points. According to the study results, the quantity of gastric, but not duodenal foam/bubbles was significantly less in the simeticone group compared to the placebo (P=0.002). The duration of endoscopy was, on average, one minute less in simeticone group versus placebo (P <0.001). Patient satisfaction with the procedure was the same in both groups. Therefore, simeticone administration before esophagogastroduodenoscopy decreases the quantity of gastric foam and bubbles and provides better visibility for the assessment of mucous membranes. It also decreases the endoscopy duration (Ahsan et al., 2011).

One randomized double-blind placebo-controlled study assessed the efficiency and tolerability of lavage by polyethylene glycol-electrolytic solution (PEG-ELS) with and without simeticone during preparation for colonoscopy in 115 patients with Crohn's disease and ulcerative colitis (Lazzaroni et al., 1993). Patients received either PEG-ELS 4 L plus placebo, or PEG-ELS 4 L plus simeticone. In 105 patients, who completed the study, the efficiency of large intestine lavage was virtually comparable for both regimens, although the addition of simeticone significantly decreased gas bubble formation in the intestine. Also, simeticone group showed significant decrease in general malaise and sleep improvement. Therefore, the use of PEG-ELS with simeticone is an efficient method of intestinal lavage, which may be used in patients with inflammatory bowel diseases. The patients tolerated well simeticone in addition to the traditional formulation (Lazzaroni et al., 1993).

Martinez-Vazquez M.A. et al. presented meta-analysis of randomized controlled clinical trials for the period from January 1960 to May 2011, noting the clinical effectiveness and tolerability of combinations of spasmolytic agents with simeticone for the treatment of Irritated Bowel Syndrome. 27 studies were identified, examining the efficiency of pinaverium bromide, mebeverine, otilonium, trimebutine, alverine, gioscine, alverine/simeticone, pinaverium/simeticone, fenoverine, and dicyclomine. In total 2585 patients were included in meta-analysis. Global improvement was 1.55 (CI 95%: 1.33–1.830). The authors concluded that the use of spasmolytic agents was more efficient than a placebo in IBS therapy, without significant adverse effects. The addition of simeticone improved the characteristics of spasmolytic agents (Martínez-Vazquez et al., 2012).

Irritated Bowel Syndrome is a functional intestinal disease, characterized by chronic abdominal pain, discomfort, abdominal flatulence, and intestinal disorders without any organic causes. At present there is no objective result of treatment efficiency in this disease. Lopez-Alvarenga J.C. et al. performed a clinical study, assessing the efficiency of IBS treatment with simeticome and pinaverium bromide. 1677 patients participated in this study, who received pinaverium bromide 100 mg and simeticone 300 mg. After administration of pinaverium bromide and simeticone the patients demonstrated a marked reduction of pain and flatulence, independently of the IBS subtype. The plateau was not achieved in 4 weeks, however, during this period a maximal improvement was achieved. Polar vector analysis showed significant improvement in patients with IBS-C during the first two weeks of treatment and stable improvement for the next two weeks (López-Alvarenga et al., 2013).

Simeticone and N-acetyl cysteine are widely used for improvement of endoscopic visibility. A one-centre prospective randomized study was carried out from September 2011 to February 2012. 1849 patients were treated prospectively in three groups: group A: 100 mg of simeticone suspension in water 5 ml; group B: 100 mg of simeticone suspension in water 100 ml; and group C: 100 mg of simeticone suspension in water 100 ml, containing 200 mg of N-acetyl cysteine. The visibility of mucous membranes was assessed in seven zones of the upper gastrointestinal tract. Total score was the general assessment of mucous membrane visibility. The upper abdominal zone had the worst visibility parameter for all groups. Total assessment of mucous membrane visibility in groups B and C was significantly lower than in group A. In group C there were significantly fewer patients, who required endoscopic lavage, compared to groups A and B. The total assessment of mucous membrane visibility for groups B and C was significantly lower than for group A during 30 minutes from the start of premedication. After more than 30 minutes of premedication, there was no significant difference in total visibility parameter of mucous membrane between the groups. Premedication, using simeticone 100 mg in water 100 ml improves endoscopic visibility. The addition of N-acetyl cysteine to simeticone in water 100 ml decreases the need for endoscopic lavage. In patients, who cannot tolerate large volumes of fluid, authors recommend administering 5 ml of simeticone suspension more than 30 minutes before endoscopic examination of upper gastrointestinal zones (Chang et al., 2014).

The combination of citrate alverine and simeticone has been used for more than 20 years in irritated bowel syndrome (IBS). In this double-blind, randomized, placebo-controlled trial 412 patients with IBS were included, who complied with the criteria ROME III, if the intensity of their pain/abdominal discomfort was a

minimum of 60 mm per 0-100 mm. The patients were randomized using an interactive voice response system for the use of alverine citrate 60 mg with simeticone 300 mg three times daily, or corresponding placebo for 4 weeks. Full analysis set included 409 patients. On week 4 the group of alverine citrate and simeticone had the lowest parameters of abdominal pain/discomfort by visual analogue scale (median: 40 mm versus 50 mm, P=0.047) and higher response level ((46.8% versus 34.3%, OR=1.3); P=0.01) compared to placebo group. Patients, who received alverine citrate and simeticone reported better global improvement of symptoms versus placebo group (P=0.0001). Therefore, combination of alverine citrate/simeticone was significantly more efficient than a placebo for the relief of abdominal pain/discomfort in IBS patients (Wittmann et al., 2010).

Reports on studies of efficiency and safety of phloroglucinol dehydrate.

Phloroglucinol (1,3,5-trihydroxybenzene) – is a non-atropinic spasmolytic, which spasmolytic effect on smooth muscles was first demonstrated in animals. It was shown that phloroglucine weakened induced contractions in gastrointestinal system. The agent is effective in the entire gastrointestinal tract. Later, the researchers studied phloroglucinol effects on contractions in isolated rat and rabbit intestines. It was established that spasmolytic properties of phloroglucinol were associated with the inhibition of catecholamine-O-methyltransferase (COMT), which enhanced the inhibiting effects of catecholamines on intestine (Inoue, 1969; Polez et al., 2024).

The pharmacokinetic profile of phloroglucinol after peroral and intravenous administration was studied in rats (Dollo et al., 1999).

In this study, the radioactivity in blood and tissues was measured after a single intravenous injection of 50 mg/kg (130 μCi/mg) of radioactively labeled phloroglucinol (^{3}H-phloroglucinol) (Keramaris et al., 2020).

Plasma elimination half-life was about 15 min. 15 minutes after the administration the highest concentration was registered in kidneys (5.9 μg/g), liver (6.0 μg/g), and intestine (4.6 μg/g). After 48 hours the concentrations in liver and muscles were, respectively, 2 μg/g and 1.1 μg/g. The amount, detected in urine and feces 48 hours after the injection corresponded to 4.2 and 22.1% of the administered dose. About 70% of administered dose of ^{3}H-phloroglucinol is not eliminated; therefore, the compound may have radio-colloidal properties and adhere to blood vessels.

Phloroglucine, given to rats at a dose of 100 mg/kg, was absorbed rapidly and completely, (Timax=30 minutes); its elimination half-life was short (about 30 minutes), and distribution volume and total clearance were high (respectively, 3.31 l/kg and 72.5 ml/min./kg) (Dollo et al., 1999). Such results suggest that phloroglucinol is widely distributed in the body, where it is rapidly metabolized.

Phloroglucinol is eliminated with urine both in unchanged form and as hydroxylated metabolites and glucuronic and sulphate conjugates, such as dimetoxy-1,3-hydroxy-5-benzene or trimetoxybenzene. These metabolites are formed in the liver by O-methylation (Keramaris et al., 2020).

Functional intestinal disorders are a complex therapeutic task for clinical practice. At present, among therapeutic options medical therapy dominates, however, none of the therapeutic strategies has a proven benefit for all patients with functional intestinal symptoms, and the treatment is tailored for the relief of principal symptoms. As it is recognized that the changes in motor activity underlie the majority of functional intestinal symptoms, spasmolytics remain the mainstay of medical treatment. Spasmolytics are recommended for the treatment of patients with abdominal pain and/or abdominal flatulence without intestinal flatulence, as the principal symptoms. As a spasmolytic, phloroglucinol has been used for decades. It has proven its efficiency for the relief of abdominal symptoms in several clinical trials. It was demonstrated that it decreased abdominal spasms, with significant decrease in the number and amplitude of phase contractions, acting directly on smooth muscle of the large intestine. In the French study of symptoms assessment and treatment of functional gastrointestinal symptoms in 1266 patients in 1999, phloroglucinol was the third out of eleven agents, used for such disorders, and 71% of patients after phloroglucinol treatment noted its efficiency.

Seventy-two patients with irritated bowel syndrome (IBS), corresponding to Rome criteria III, were randomized 1:1 in the double-blind design in parallel groups, to obtain phloroglucinol or placebo for 2 weeks. The patients were followed up for 1 week after the end of treatment. The principal result was the share of patients, who responded to treatment, determined as patients with "moderate or larger improvement" according to general subject assessment for at least 1 week during a 2-week treatment period. The secondary results included the share of such patients during 3-week period, including 1 week of follow-up, IBS symptoms (abdominal pain/discomfort, diarrhea, defecation urgency, mucus in feces, abdominal distension, and meteorism), stool frequency and consistency, and life quality with IBS. The share of responders during 2-week treatment period was, as a rule, higher in the phloroglucinol group versus placebo, however, without reaching statistical significance (55.6% versus 30.6%, P=0.056). The share of responders during 3-week period was significantly higher in

the phloroglucinol group versus placebo (61.6% versus 30.6%, P=0.013). Individual assessments of symptoms, IBS, stool frequency, and consistency showed tendency to improve in the phloroglucinol group, however, without statistical significance versus placebo group. No serious adverse events were registered in both groups (Shin et al., 2020).

There are many clinical proofs of phloroglucinol efficiency for symptom improvement in literature, caused by functional intestinal disorders.

A randomized double-blind placebo-controlled study evaluated phloroglucinol safety and efficiency in 40 patients with IBS (17 males, 23 females) (Rautereau et al., 1987). The treatment was given orally (two tablets of phloroglucinol or placebo twice daily) for two months. The principal efficiency endpoints were the frequency of spontaneous pain episodes (number of episodes per day or week), and the intensity of such episodes (assessment: 0=zero; 1=low, 2=medium, 3=high) during treatment. Safety analysis was based on adverse effects, registered throughout the study. In total, 33 patients were included in intent-to-treat population, one phloroglucinol patient was excluded due to poor compliance, and the data was absent for the full assessment of six other patients (six patients with phloroglucinol and three control patients). Both treatment groups were comparable at baseline. The intensity of pain episodes was significantly lower in the phloroglucinol group versus placebo group, both after one (D30), and after two months of treatment (D60) (ANOVA, $p<0.05$) Pain episodes were also significantly less frequent in phloroglucinol group versus control (three-way ANOVA, $p<0.01$).

The researchers performed an open (quasi-interventional) study to assess phloroglucinol in patients with irritated bowel syndrome. For the period from February 2004 to September 2004 100 patients were enrolled in the study, who consulted Gastroenterology Clinics of Aga Khan University Hospital for IBS, determined by Rome criteria II, and received outpatient treatment. Phloroglucinol (Himont) 50 mg was used perorally three times daily for two months. The symptoms were assessed before and during treatment by questionnaire. A hundred patients were included in the study. They included 61% (61/100) males and 39% (39/100) females. The average patient age was 41 +/- 14 years. Sixty-eight patients completed the study, and 28 patients withdrew. During phloroglucinol treatment the authors registered general statistically significant improvement in abdominal pain ($p<0.001$), daily stool frequency ($p<0.001$), defecation urgency ($p<0.001$), mucus excretion through rectum ($p<0.001$), sensation of incomplete emptying ($p=0.001$), and abdominal distention ($p=0.001$). However, both genders did not show a response to tension characteristics during defecation ($p=0.676$). The analysis of response to treatment by genders showed statistically significant improvement of incomplete emptying only in females ($p=0.003$). The authors concluded that a phloroglucinol dose of 50 mg three times daily is efficient and well-tolerated in IBS patients. Phloroglucinol improved the majority of IBS symptoms (Jafri et al., 2006).

Pain and spasms of the urinary and biliary tract deteriorate quality of life. Treatment with analgesics, such as non-steroidal anti-inflammatory drugs and modulators of parasympathetic system is not always tolerated and often requires additional therapeutic options. The aim of this analysis was to assess the pharmacokinetics and efficiency of peroral and parenteral products based on phloroglucinol for decreasing pain and spasms, associated with renal or biliary colics. Four multi-centre, open, randomized, comparative studies of phase 3 were conducted to assess clinical efficiency and safety in patients with pain and spasms of urinary or biliary tract. The respective patients were randomized to receive phloroglucinol peroral or as intramuscular (i/m)/intravenous (i/v) injections and reference product dexketoprofen for urinary spasms and pain, NSAID metamizol, or reference scopolamine-based product for biliary colics. The primary results were symptoms and observed spasm frequency, while the secondary results were duration of improvement, or time between the drug administration and repeated manifestation of symptoms. The groups were compared by quantitative attributes with a T-test for independent samples, or the Mann-Witney criterion. Intra-group comparisons were performed with the Wilkoxon test or T-test for dependent samples. Qualitative attributes were analyzed by Pearson $\chi 2$ criterion and Fisher's exact test. The study results allow concluding that peroral and parenteral phloroglucinol-based products have the same efficiency for decreasing pain and spasms, associated with renal and biliary colics, as the modern therapeutic options. Therefore, phloroglucinol may be considered useful for treatment of pans and spasms, associated with urinary and biliary colics (Corvino et al., 2022).

One placebo-controlled study showed that phloroglucinol and trimethyl phloroglucinol were non-specific spasmolytics, decreasing pain in patients with IBS (Annaházi et al., 2014). Another study was designed to assess phloroglucinol efficiency in combination with its methylated derivative trimethyl phloroglucinol for pain intensity during acute exacerbation of IBS-associated pain for one-week period of treatment (Chassany et al., 2007). IBS patients, who sought medical aid due to exacerbation of abdominal pain, were randomized to

obtain phloroglucinol/trimethyl phloroglucinol (62.2 mg phloroglucinol + 80 mg trimethyl phloroglucinol, two tablets three times daily) or placebo for seven days. Patients were included, if they felt pain with minimal intensity 40 (by 100-mm visual analogue scale) and experienced the pain a minimum of two days a week before the induction. Intent-to-treat population included 300 patients (73% females) aged 46.9 ± 14.8 years. Relative decrease of pain intensity by day 7 was 57.8 ± 31.7% versus 46.3 ± 34.7%, and the percentage of patients with a pain intensity decrease of minimum 50% was 62% versus 47%, respectively, in the groups of phloroglucinol/trimethyl phloroglucinol and placebo. It was shown that one week of treatment with phloroglucinol/trimethyl phloroglucinol significantly decreased pain intensity in patients with irritated bowel syndrome.

The report of the Tura Regional Pharmacovigilance Centre, dated July 2008 assessed 62 serious adverse allergic reactions between 1995 and 2006 in patients, using peroral forms of phloroglucinol. The reactions included: 11 cases of anaphylactic shock, 18 cases of angioedema, 3 cases of urticaria, 6 cases of skin vasculitis, 11 cases of skin rash, 2 cases of pruritis, 2 cases of acute generalized exanthematous pustulosis, 7 cases of bullous rash, including 4 cases of Lyell's syndrome, and 1 case of anaphylactic shock after phloroglucinol suppository. These adverse effects were mentioned for injection phloroglucinol-containing product, however, not for peroral products.

Analytical summary of the efficiency and safety studies of the simeticone and phloroglucinol dihydrate combination. *Efficacy and safety aspects during a clinical study.* It should be noted that simeticone does not possess any pharmacological properties; it just physically affects gastrointestinal gases. Therefore, it does not influence the pharmacological effects of phloroglucinol.

After oral use, phloroglucinol is rapidly absorbed and metabolized during the first pass through the liver and is eliminated as metabolites mostly via urine. Time to maximal plasma concentration T_{max} – 1 hour, with C_{max} 2.74 mg/ml, and the elimination half-life $T_{1/2}$ is 2 hours. Its systemic bioavailability after peroral administration is 30%.

After peroral use, phloroglucinol dihydrate is easily absorbed, primarily metabolized in liver, and is excreted mostly as metabolites in urine. Time to maximal plasma concentration T_{max} is 1 hour, C_{max} is 2.74 mg/ml, and the elimination half-life $T_{1/2}$ is 2 hours. The systemic bioavailability of phloroglucinol dihydrate is 30% after oral administration. Clinical studies confirm the relaxing effects of phloroglucinol dihydrate on smooth muscle of the gastrointestinal tract. Phloroglucinol dihydrate inhibits excessive enterokinesis of segmental and large intestine, which usually develops in patients with functional intestinal disorders, as a reaction to meals. Simeticone is a non-toxic inert silicon surface-active substance that prevents formation and promotes collapsing of gas bubbles. Due to the decrease in liquid surface tension, the combination of these active substances causes the melting of gas bubbles in gastrointestinal tract, which induces physiological dissipation and emission of gas. Simeticon prevents gas-produced defects during ultrasound or radiological visualization. Simeticone is not absorbed in the body, it passes through gastrointestinal tract and is eliminated in unchanged form (Wu et al., 2010).

Clinical efficiency of a combination of simeticone and phloroglucinol dihydrate for the treatment of functional intestinal symptoms was demonstrated in several trials during the last decades. One of them was carried out in the Ukrainian Research and Practical Centre of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of the Ministry of Health of Ukraine. The study was aimed on estimation of the simeticone and phloroglucinol combination efficacy and safety in patients with irritable bowel system (IBS).

The study involved 62 patients with IBS aged 23 to 60 years (mean age 38 ± 16 years), from them 42 women and 20 men. In all involved patients with IBS, organic intestinal pathology was excluded by means of colonoscopy, and the IBS diagnosis was determined in accordance with the Rome criteria IV. The patients were randomized into two groups depending on the treatment scheme: the research group (32 patients) and the control group (30 patients). In the control group, patients with IBS have been treated by the basic therapy, which involved therapy by loperamide on demand (IBS with diarrhea), psyllium on demand (IBS with constipation) and antispasmodic (mebeverine 1 capsule twice a day) for 1 month. Patient's diet predicted restriction of fermentable oligo- and monosaccharides. In the research group, patients with IBS have been treated with the simeticone and phloroglucinol combination instead of mebeverine against the background of basic therapy (2 capsules thrice a day before meals, during 1 month).

It was determined that 15 of 30 patients in the control group (50%) reacted positively to mebeverine treatment, while 20 of 32 patients in the main group (62.5%) reacted positively to the simeticone and phloroglucinol combination treatment, which was significantly higher ($p < 0.05$). In particular, the severity of pain and diarrheal syndromes according to the GSRS questionnaire after the simeticone and phloroglucinol combination treatment was significantly lower than in patients of another group. Quality of life indicators, such as

general health, life and physical activity, in the main group were statistically significantly higher than in the control group. No significant adverse side effects were detected when taking the simeticone and phloroglucinol combination. None of the patients with IBS without constipation experienced constipation during treatment with this drug (Tkach, 2020).

Safety aspects of the fixed combination of simeticone and phloroglucinol dihydrate. According to information from the EudraVigilance database (source: https://www.adrreports.eu/en/search.html), which received information from the European Medical Agency, for the combination of simeticone and phloroglucinol dihydrate 95 reports were presented on suspected adverse events (Fig. 1–3).

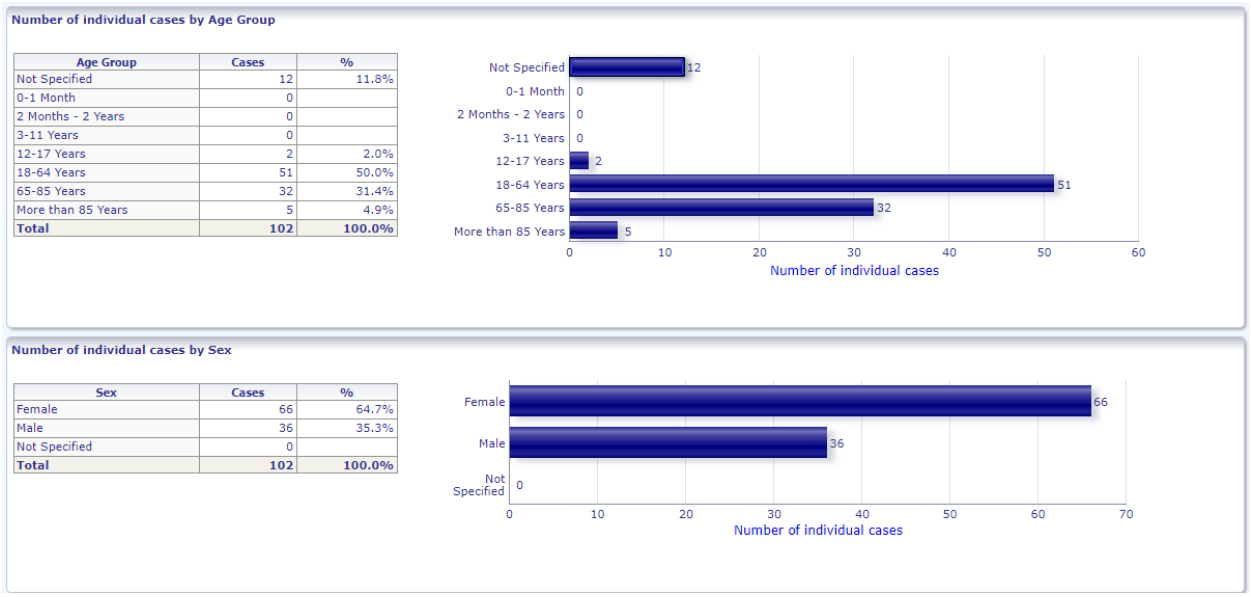

Fig. 1. General characteristics of individual cases for the fixed combination according to the EudraVigilance database (up to April, 14th, 2024)

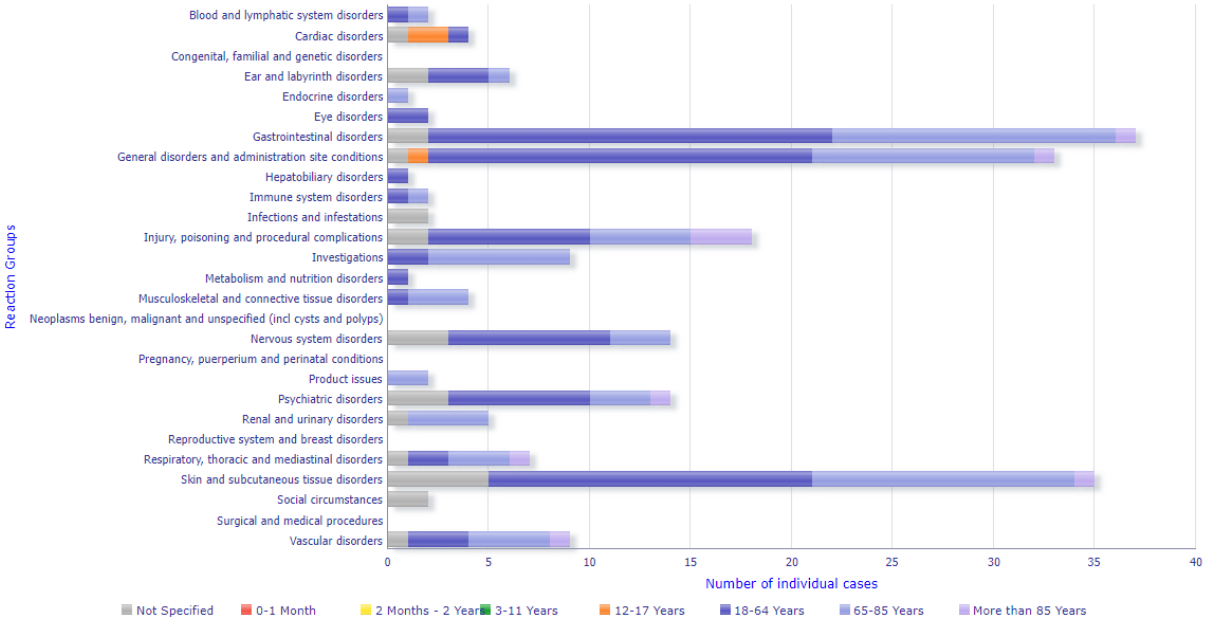

Fig. 2. Number of individual cases for the fixed combination by reaction groups (age groups) according to the EudraVigilance database (up to April, 14th, 2024)

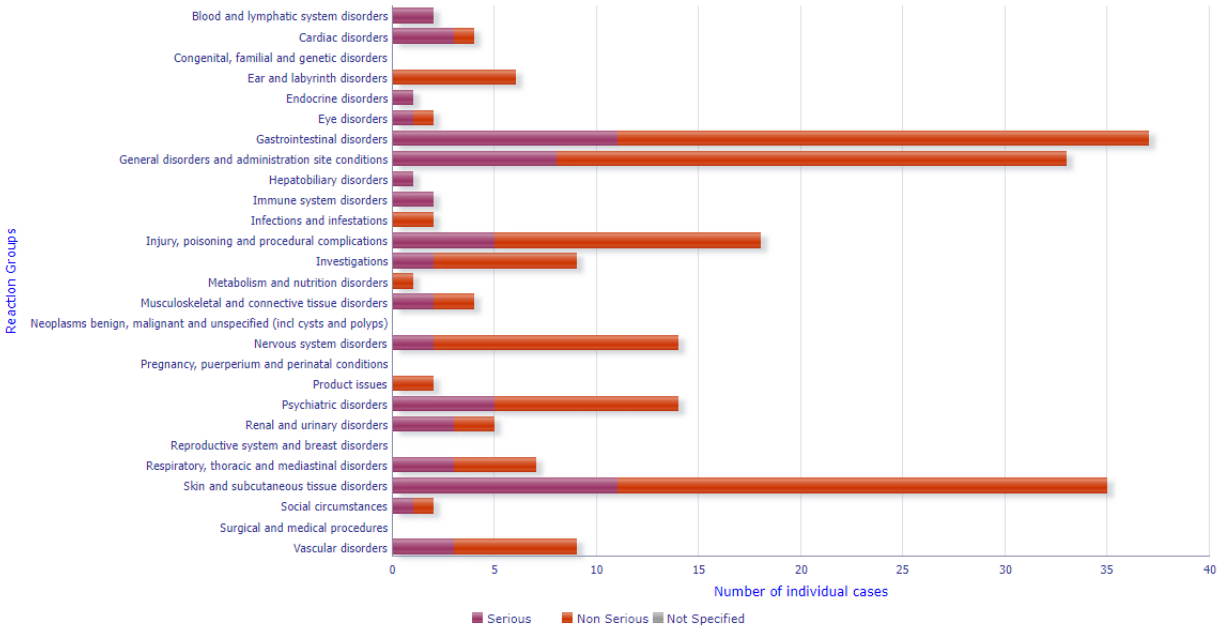

Fig. 3. Number of individual cases for the fixed combination by reaction groups (seriousness) according to the EudraVigilance database (up to April, 14th, 2024)

Considering the above data, the following adverse effects of this combination were registered. Serious adverse events: blood and lymphatic system disorders (2 cases), cardiac disorders (3 cases), endocrine disorders (1 case), eye disorders (1 case), gastrointestinal disorders (11 cases), general disorders and administration site conditions (8 cases), hepatobiliary disorders (1 case), immune system disorders (2 cases), injury, poisoning, and procedural complications (5 cases), investigations (2 cases), musculoskeletal and connective tissue disorders (2 cases), nervous system disorders (2 cases), psychiatric disorders (5 cases), renal and urinary disorders (3 cases), respiratory, thoracic and mediastinal disorders (3 cases), skin and subcutaneous tissue disorders (11 cases), social circumstances (1 case), and vascular disorders (3 cases). Non-serious adverse events: cardiac disorders (1 case), ear and labyrinth disorders (6 cases), eye disorders (1 case), gastrointestinal disorders (24 cases), general disorders and administration site conditions (23 cases), infections and infestations (2 cases), injury, poisoning and procedural complications (12 cases), investigations (6 cases), musculoskeletal and connective tissue disorders (2 cases), nervous system disorders (11 cases), product issues (2 cases), psychiatric disorders (9 cases), renal and urinary disorders (2 cases), respiratory, thoracic and mediastinal disorders (3 cases), skin and subcutaneous tissue disorders (20 cases), social circumstances (1 case), and vascular disorders (5 cases).

According to the data, reviewed by Transparency Committee in France (2017), for the original fixed combination the conclusions were made that for the reporting period from 2014 to 2017 no changes in the Summary of Product Characteristics were introduced in the sections “Adverse effects”, “Special warnings and precautions for use” or “Contraindications”. From the time of the last assessment by the Committee on 04.02.2014, the place of the original fixed combination in therapeutic strategy remained unchanged. The medicinal product is adapted to the conditions of prescription according to its indications, dosage, and duration of treatment. This is the first line product after a healthy lifestyle and diet (Commission, 2017).

Reports on serious cases. One case of drug delivery error was reported – confusion between the original fixed combination and methotrexate in a 35-year-old woman. She reported abdominal pain, stomatitis, and thrombopenia after 5 days of treatment with a daily dose of methotrexate 15 mg (6 capsules by 2.5 mg daily). The patient discovered a medication error herself and was immediately transported to the Intensive Care Department. The result was favorable. The case report was called “probably associated” with methotrexate.

DRESS syndrome was reported in a 70-year-old woman, who used several drugs, including the original fixed combination for 2–3 months. She was hospitalized due to erythrodermia, associated with bullous lesions, mucous membrane lesions, hypotension, and dehydration.

DRESS syndrome was diagnosed, and the most suspected product was drospirenone and estetrol combination. The result was favorable.

A case of drug delivery error between the original fixed combination and methotrexate was registered in an 88-year-old male. He reported abdominal pain after 3 days of treatment with daily dose of methotrexate 7.5 mg (3 capsules by 2.5 mg daily). The cardiologist discovered the medication error, and the patient was immediately hospitalized for abdominal surgery.

Reports on non-serious cases. A case of diffuse exanthema, associated with vesicles without fever and changes in general condition was reported in a 65-year-old woman, who received 3 days methotrexate in 2 capsules daily. Recovery was registered after the original fixed combination cessation. Patch tests gave negative results for methotrexate ingredients. The case report was called "unlikely associated".

There was a case of nausea and malaise in a woman, who received the original fixed combination 6 capsules daily. The reported case was not medically confirmed and was considered undocumented.

3 cases of delivery error with the same product methotrexate are known and followed up by two companies. Such confusion was very rare, as the packages and indications for each product were very different.

During the covered period from January 2006 to July 2008, the original fixed combination was not withdrawn from the market, also it was not subject to suspensions or restrictions of distribution. No safety changes were introduced to the text of the summary of product characteristics (SPC) for the original fixed combination (changes in sections, concerning warnings, precautions, interactions, and overdose). All these data suggest that the original fixed combination is well-tolerated.

Conclusions on benefit-risk ratio for the combination of active substances simeticone and phloroglucinol dihydrate. Functional intestinal disorders are some of the most common diseases, registered by primary care doctors and specialized gastroenterological clinics. Notwithstanding their benign character, these diseases substantially affect health-related quality of life (Chang, 2004). At present, among therapeutic options for functional intestinal disorders medical therapy prevails and the treatment, as a rule, is aimed at relief of dominating symptoms (Quartero et al., 2005).

As it is recognized that the changed motility underlies the majority of intestinal disorders, spasmolytics remain a mainstay for pharmacological treatment (De Ponti et al., 1998). Spasmolytic agent phloroglucinol has been used for decades and has proven its efficiency for the relief of these symptoms in several clinical trials (Louvel et al., 1996; Jafri et al., 2006).

The fixed combination is an oral medicinal product, containing both phloroglucinol and simeticone, marketed since 1996 as additional remedy for treatment of functional intestinal disorders, in particular, meteorism and diarrhea (Golembiovska, et al., 2019; Tkach, 2020).

The efficiency and safety of the fixed combination have been proven for many years of its use. Its adverse effects are mentioned in SPC (Summary of product characteristics, 2017). As no large-scale clinical trials were performed to study the original fixed combination safety in pregnancy and breastfeeding, the product should not be prescribed to pregnant or breastfeeding females. Therefore, the fixed combination is effective and safe therapeutic product for additional treatment of functional intestinal symptoms.

Conclusions. The proofs of efficiency and safety, obtained in clinical trials demonstrate that the combination of phloroglucinol dihydrate/simeticone is an effective treatment of functional intestinal symptoms, both concerning the development of general intense symptoms, and the following specific symptoms, such as "sensation of discomfort" and "other digestive symptoms".

The efficiency and safety of the fixed combination are proven by many years of its use. According to the international database VigiAccess (statistical data on suspected side effects of drugs and vaccines, reported in the framework of WHO Programme for International Drug Monitoring), at least for the period from 2014 up to 2024, for the original fixed combination, no new (previously unidentified) adverse effects were reported.

According to the data, reviewed by Transparency Committee in France (2017), for the fixed combination the conclusions were made that for the reporting period from 2014 to 2017 no changes in the Summary of Product Characteristics were introduced in the sections "Adverse effects", "Special warnings and precautions for use" or "Contraindications". From the time of the last assessment by the Committee on 04.02.2014, the place of the fixed combination in therapeutic strategy remained unchanged. The medicinal product is adapted to the conditions of prescription according to its indications, dosage, and duration of treatment. This is the first line product after a healthy lifestyle and diet.

According to the analyzed data, presented in adverse effects databases, scientific literature sources, and published studies, no new information on safety was revealed that would change the safety profile for the combination phloroglucinol dihydrate/simeticone. In the literature sources and the published information for the period of use of active substance combination simeticone and phloroglucinol dihydrate globally (from 1996) and in Ukraine (from 2011) no new adverse effects were registered.

Therefore, the medicinal product based on simeticone and phloroglucinol dihydrate is effective and safe therapeutic product for additional treatment of functional intestinal symptoms.

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