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Actitan: A Natural Complex for Managing Diarrhea—Insights from Cross-Sectional Survey Research Involving Patients, Pharmacists and Physicians

Roberto Cioeta [1], Paola Muti [2,3], Marta Rigoni [2,3], Andrea Cossu [1,*] and Emiliano Giovagnoni [1]

[1] Aboca SpA, 52037 Sansepolcro, Italy; rcioeta@aboca.it (R.C.); egiovagnoni@aboca.it (E.G.)
[2] Department of Biomedical, Surgical and Dental Sciences, University of Milan, 20122 Milan, Italy; paola.muti@unimi.it (P.M.); marta.rigoni@unimi.it (M.R.)
[3] I.R.C.C.S. Multimedica, 20099 Milan, Italy
* Correspondence: acossu@aboca.it

Abstract: Diarrhea continues to be a global health problem as acute diarrhea carries the risk of dehydration, while both acute and chronic diarrhea can significantly affect patients' quality of life and reduce productivity. The innovative medical device Actitan, which consists of a complex of natural molecules, could be an effective option for the treatment of diarrhea from various causes. The aim of this post-market cross-sectional study was to evaluate the perceived efficacy, safety and usage pattern of the two formulations for adults (Actitan-P) and children (Actitan-F) among patients/child caregivers, physicians and pharmacists. Participants completed online questionnaires with closed multiple-choice questions that were rated on a verbal 5-point Likert scale. These surveys were conducted via the online platform Real World Data, which provides digital questionnaires for patients, doctors and pharmacists. Two separate surveys were conducted for the two formulations, with a total of 2630 participants (1488 participants for Actitan-P and 1142 participants for Actitan-F). Overall, the results indicate a high level of efficacy and safety of the product. In the case of Actitan-F, more than 96% of caregivers rated safety as good or excellent, and over 92% rated efficacy as good or excellent. Actitan-P also received positive feedback: nearly 86% of patients reported good/excellent efficacy, and more than 93% rated safety as good or excellent. These positive evaluations were confirmed by physicians and pharmacists, who also did not report adverse effects. In summary, this study confirms the role of Actitan as a safe and effective option for the treatment of diarrhea of different causes and in different patient groups, including young children.

Keywords: acute diarrhea; chronic diarrhea; natural substance-based medical device; safety; effectiveness; digital survey

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1. Introduction

Diarrhea, which is characterized by an increase in volume, water content, or the frequency of bowel movements, is one of the most common gastrointestinal disorders worldwide [1]. According to the World Health Organization (WHO), it is defined as "the passage of three or more loose or liquid stools per day, or more often than is usual for the individual" [2]. Diarrhea can be classified according to its duration: acute diarrhea typically begins suddenly, lasts less than 14 days, and is often caused by viral infections, which are more common during the winter months [3–5]. If the symptoms persist for more than 28 days, the condition is considered chronic and can have various causes, e.g., infectious, iatrogenic, functional or autoimmune diseases [3,4,6].

Diarrhea is essentially the result of an imbalance between the absorptive and secretory processes within the intestinal epithelium. From a pathophysiological point of view, this may be due to an increase in luminal osmolarity, which allows water to enter the intestine (osmotic diarrhea), activate the stimulation of fluid secretion into the intestinal lumen

(secretory diarrhea) and cause inflammatory conditions, and motility disorders. These factors can interact differently in individual patients [3,7–9].

An accurate diagnosis is crucial for the precise treatment and management of this condition. Regardless of the underlying cause, the rehydration and supplementation of essential minerals are the cornerstones of diarrhea treatment [7,10]. Various antibiotics can be used for infectious diarrhea, but their selection should be based on the laboratory diagnosis of the pathogenic organism. Although antibiotics can effectively reduce the duration and intensity of diarrhea caused by intestinal infections, they often have a delayed effect that cannot prevent dehydration. They can also harm patients by disrupting the gut microbiota, especially in children [10]. Antidiarrheal drugs, including antimotility agents and antisecretory drugs, provide effective symptomatic therapy and may help reduce the inappropriate use of antibiotics [10–14]. Although these drugs are widely used and effective, they are not suitable for long-term use. In addition, their highly specific clinical target (antisecretory agents), potential adverse effects and narrow therapeutic index (antimotility agents) have further limited their recommendation [11,12].

The availability of an effective, non-pharmacological therapeutic option for the treatment of diarrhea, therefore, meets a clear medical need, particularly in children, the elderly and individuals undergoing multiple drug treatments for whom pharmaceutical treatment is not an option or who wish to avoid it [15–19].

Actitan-P and Actitan-F (Lenodiar Adult and Pediatric, respectively; Aboca S.p.A., Sansepolcro, Italy) are substance-based medical devices (SBMDs) [20–22] for the treatment of diarrhea while maintaining intestinal physiology and preventing constipation. They consist of a natural tannin-based complex that can reduce the frequency of bowel movements, normalize stool consistency and act as a protective agent on the surface of the intestinal mucosa to reduce stimulation by exogenous harmful factors. In addition, this innovative complex acts as a free radical scavenger to counteract inflammation of the mucous membrane [23,24]. Both Actitan-P and Actitan-F are recommended for the treatment of diarrhea caused by various factors. The use of Actitan-P is also suggested as part of combination therapy for chronic diarrhea, such as irritable bowel syndrome (IBS), functional diarrhea and inflammatory bowel disease (IBD) [21].

As Actitan-P and Actitan-F are medical devices that are frequently used without medical advice, it is essential to assess real-world data (RWD) on their safety and efficacy. This evaluation is required under the new EU Medical Device Regulation (EU) 2017/745, which introduced updated criteria for the authorization, classification and post-market surveillance of the safety and performance of medical devices [20]. Accordingly, this large-scale cross-sectional study aimed to assess the perceived efficacy, safety and pattern of use of adult and pediatric formulations by patients/child caregivers, physicians and pharmacists.

2. Results

2.1. Patients/Child Caregivers

A total of 621 patients participated in the Actitan-P survey, 86.8% (N = 539) of whom were women. Most patients were adults aged between 31 and 50 years (59.1%, N = 367). The other age groups were distributed as follows: 1 subject (0.2%) between 14 and 16 years, 70 (11.3%) between 17 and 30 years, 157 (25.3%) between 51 and 64 years and 26 (4.2%) older than 64 years. Most patients practiced self-medication (84.5%, N = 525) and used the product to treat acute diarrhea (80.0%, N = 497). A smaller group (15.6%, N = 97) used it for chronic diarrhea, mainly for functional disorders (irritable bowel syndrome and functional diarrhea, FD). The distribution of the different chronic diarrheal disorders for which the product was used is shown in Figure 1A.

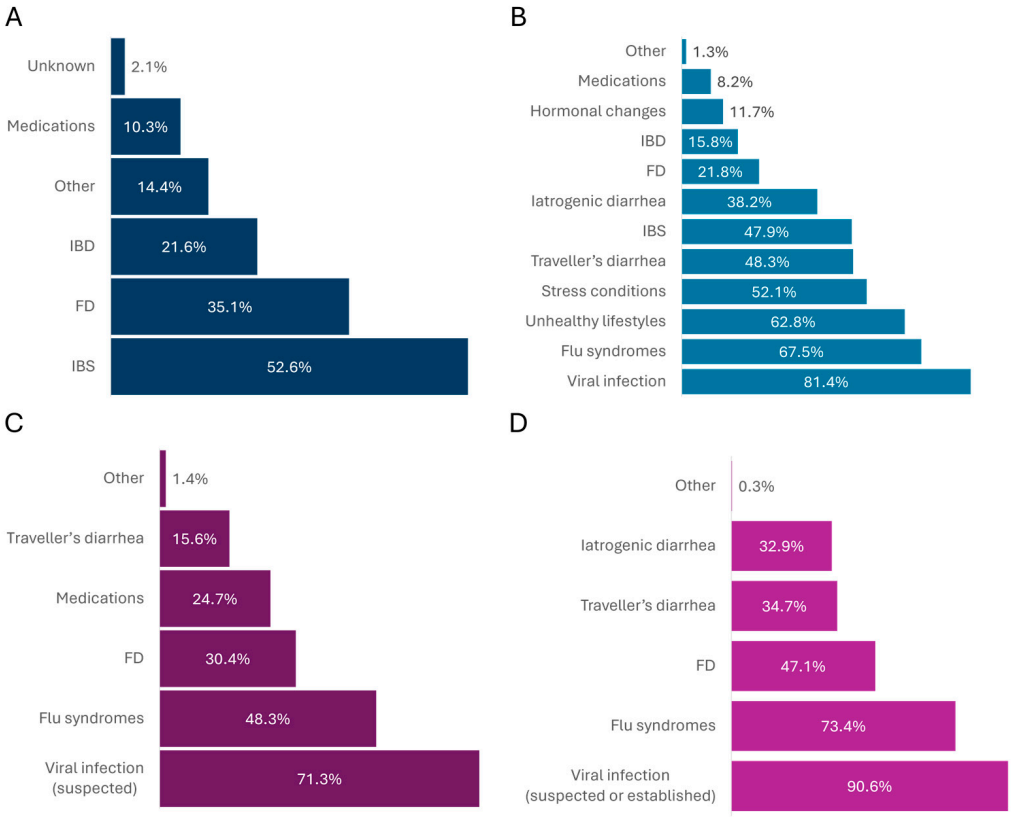

Figure 1. Causes of diarrhea for which Actitan was used/prescribed. (**A**,**B**): Distribution of different chronic diarrheal illnesses (**A**) and diarrheal illnesses of any duration (**B**) for which Actitan-P (adult formulation) was used/prescribed, as reported by patients (97 respondents) and physicians (317 respondents in total), respectively. (**C**,**D**): Distribution of different diarrheal conditions for which Actitan-F (pediatric formulation) was used/prescribed, as reported by child caregivers (352 respondents) and physicians (331 respondents), respectively. Abbreviations: irritable bowel syndrome (IBS); functional diarrhea (FD); and inflammatory bowel disease (IBD). All results in the figure refer to multiple-response questions, with the percentages indicating the proportion of respondents who selected each response.

Stress (64.3%, N = 308), diet and lifestyle (49.3%, N = 236) and hormonal changes (31.7%, N = 152) were the most frequently cited causes of acute conditions.

Most patients reported that taking Actitan-P led to a great (49.2%, N = 292) or extreme (26.3%, N = 156) improvement in their diarrhea symptoms. Most subjects (60.6%, N = 360) noticed a positive effect within 12 h, while only 2.2% (N = 13) noticed no improvement. Accordingly, the effectiveness of the products was rated as good (47.3%, N = 281) or excellent (38.2%, N = 227) in most cases (Figure 2A).

The majority of patients associated taking Actitan-P with a good (43.9%, N = 261) or excellent (25.9%, N = 154) improvement in quality of life (Figure 3A), particularly in terms of freedom to eat (46.7%, N = 260), improvement in mood (42.4%, N = 236) and reduction in anxiety (36.3%, N = 202). In addition, almost all respondents (93.1%, N = 578) rated safety and tolerability as good or excellent, and only one case (0.2%) received a poor rating. Only one non-serious adverse effect (constipation) was reported (Figure 3B).

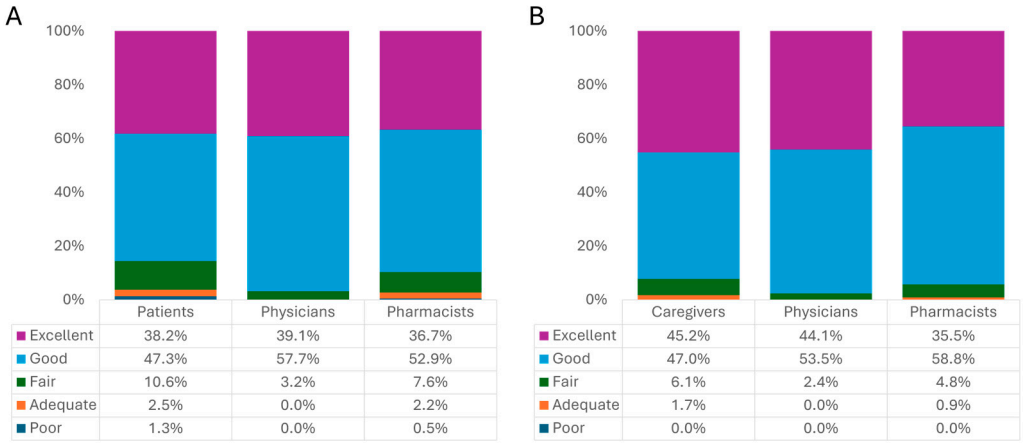

Figure 2. Effectiveness. (**A**) Efficacy of Actitan-P as reported by adult patients (594 respondents) and physicians (317 respondents and pharmacists (550 respondents). (**B**) Efficacy of Actitan-F as rated by child caregivers (347 respondents), physicians (331 respondents) and pharmacists (459 respondents). All results in the figure refer to single-response questions.

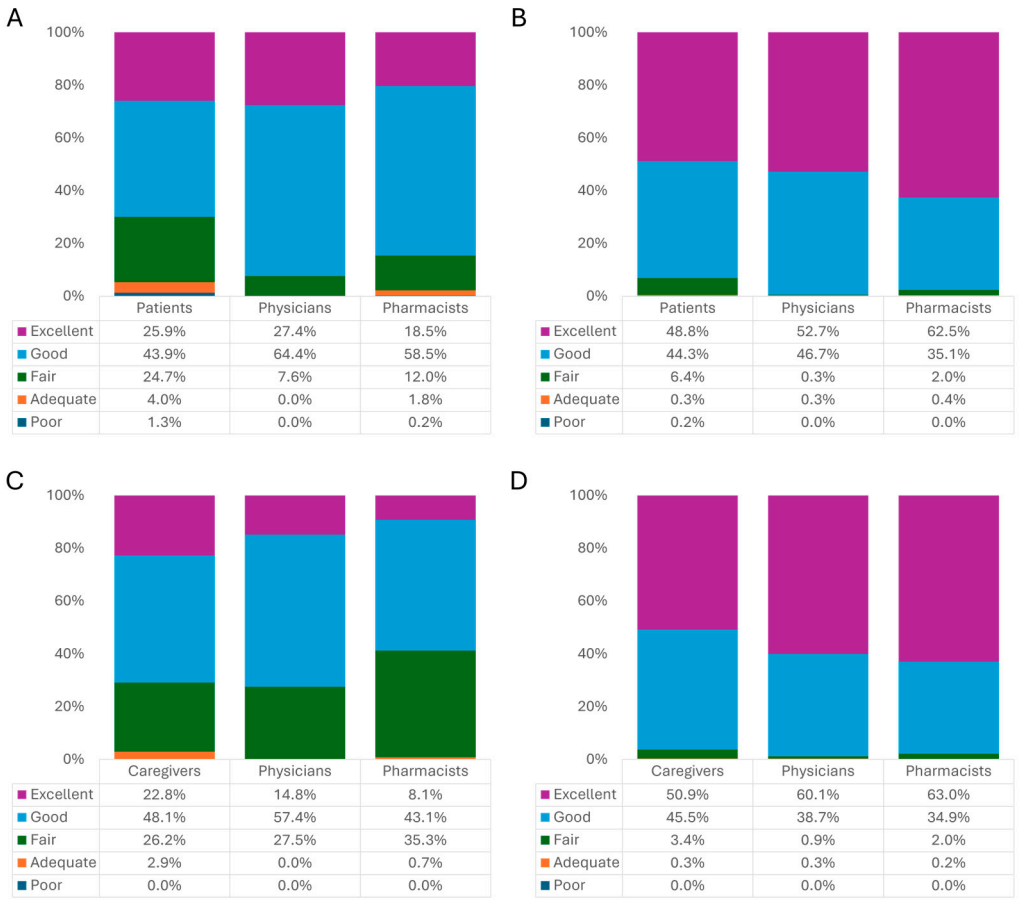

Figure 3. Effects on quality of life and safety/tolerability. (**A**,**B**): Improvement in quality of life (**A**) following the use of Actitan-P (adult formulation) and product safety and tolerability (**B**) as assessed by the responder cohorts indicated (total number of respondents: 594 and 621 patients, improvement in quality of life and safety/tolerability, respectively; 317 physicians; 550 pharmacists). Group A's charts do not include respondents who indicated "I don't know" (0.6% of physicians and

8.9% of pharmacists). (**C**,**D**): Improvement in children's quality of life (**C**) following the use of Actitan-F and the safety and tolerability of the product (**D**) as assessed by the indicated respondent cohorts (total respondents: 347 and 352 child caregivers, improvement in quality of life and safety/tolerability, respectively; 331 physicians; 459 pharmacists). All results in the figure refer to single-response questions. Group C's charts do not include respondents who indicated "I don't know" (0.3% of physicians and 12.9% of pharmacists).

Most subjects (>90%) rated the clarity of the indications, instructions for use and warnings on the product packaging and leaflet as excellent or good. Overall, 90.9% (N = 540) of patients adhered to the recommended dosage of two capsules 2–3 times daily, and a significant proportion of respondents reported probiotics (63.3%, N = 378) as other products for the treatment of diarrhea (Figure 4A).

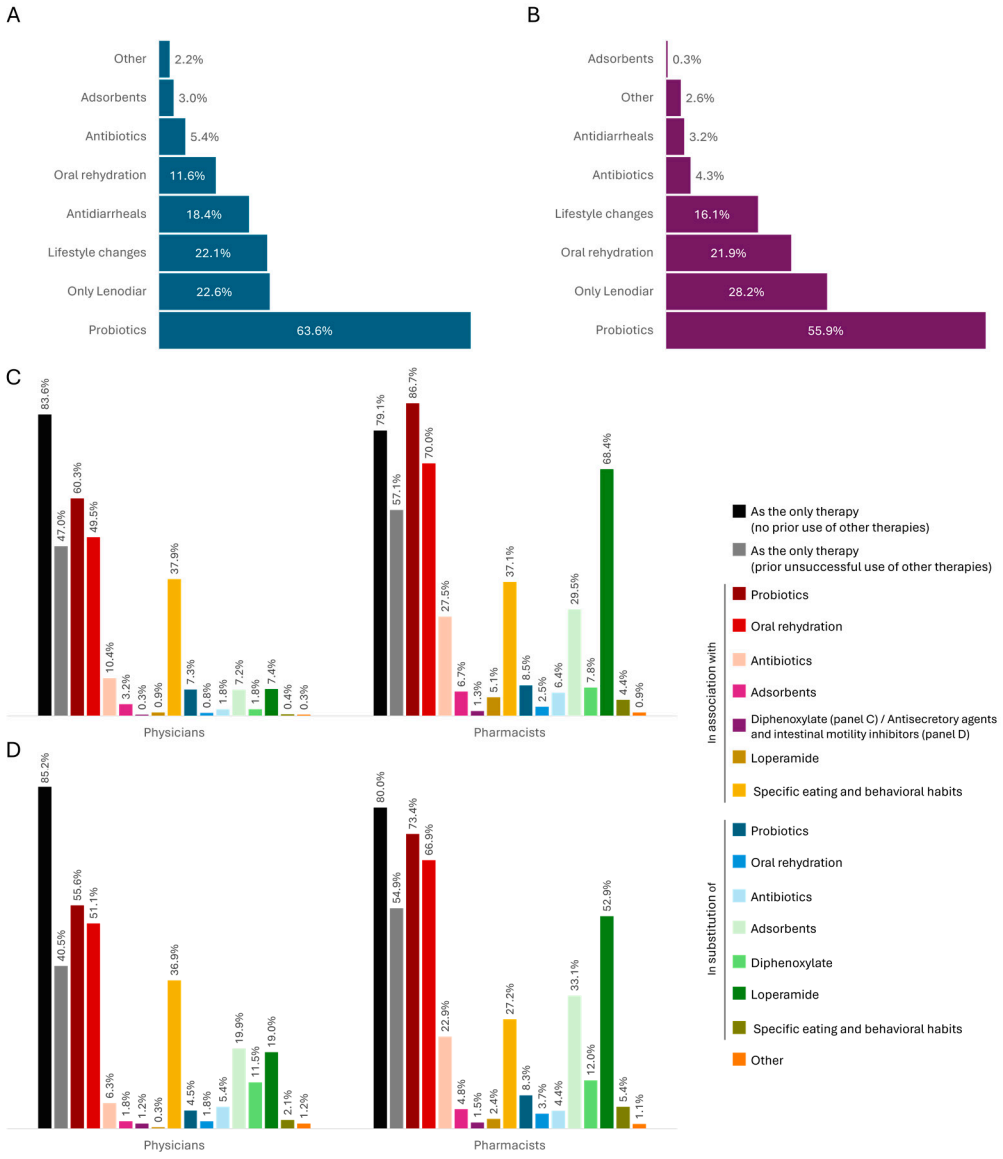

Figure 4. Products/interventions for the treatment of diarrhea. (**A**,**B**): Distribution of different products/interventions used by adult patients (594 respondents) and child caregivers (347 respondents), respectively, to treat diarrhea. (**C**,**D**): Prescribed modalities of Actitan-P (adult formulation) and Actitan-F (pediatric formulation) by physicians (317 respondents for the adult formulation and

331 respondents for the pediatric formulation) and pharmacists (550 respondents for the adult formulation and 459 respondents for the pediatric formulation), respectively. All results in the figure refer to multiple-response questions, with the percentages indicating the proportion of respondents who selected each response. Respondents who stated "I don't know" (2.2% of pharmacists) are not included in the figures.

Three hundred and fifty-two child caregivers participated in the Actitan-F survey. The product was administered almost equally to male (56.0%, N = 197) and female children (44.0%, N = 155), with the most common age group being 7–12 years (36.6%, N = 129). The other age groups were distributed as follows: 106 children (30.1%) between 4 and 6 years, 82 (30.1%) between 2 and 3 years and 26 (7.4%) were 1 year old. The product was primarily used to treat acute diarrhea (Figure 1C), in most cases (63.1%, N = 222) without consulting a physician, and the majority of caregivers found the product to be greatly (34.3%, N = 119) or extremely (42.4%, N = 147) easy to administer.

Most caregivers reported a great (48.4%, N = 168) or extreme (34.4%, N = 119) improvement in their child's diarrhea after using Actitan-F. Most respondents (59.6%, N = 207) noticed a positive effect within 12 h, while only one caregiver (0.3%) noticed no improvement. Therefore, the effectiveness of the products was rated as good (47.0%, N = 163) or excellent (45.2%, N = 157) in most cases (Figure 2B). It was also reported that a significant percentage of children were greatly (28.2%, N = 98) or extremely (32.3%, N = 112) satisfied with the taste of the product.

The majority of caregivers associated the use of Actitan-F with a good (48.1%, N = 167) or excellent (22.8%, N = 79) improvement in their child's quality of life (Figure 3C), and almost all participants (96.4%, N = 339) rated the safety and tolerability of the product as good or excellent (Figure 3D), with no interactions or side effects reported.

The clarity of the information on the package/insert regarding indications, instructions for use and warnings was rated as excellent or good by the vast majority of caregivers (>95%). The product was mainly administered at a dosage of two sachets per day (47.8%, N = 166), followed by one sachet per day (30.5%, N = 106), three sachets per day (16.7%, N = 58) and four sachets per day (4.3%, N = 15). A significant proportion of respondents reported probiotics (55.9%, N = 194) as other products used to treat their child's diarrhea (Figure 4B).

2.2. Physicians

A total of 317 physicians took part in the Actitan-P survey, of whom around a third (32.8%, N = 104) were general practitioners. The doctors mainly prescribed the product for acute diarrhea (97.5%, N = 309), followed by chronic diarrhea (37.9%, N = 120). The most common causes of acute diarrhea were viral infections (81.4%, N = 258) and flu syndromes (67.5%, N = 214). The distribution of different diarrheal illnesses of any duration for which the adult formulation was prescribed is shown in Figure 1B.

The efficacy of the product was rated as good (57.7%, N = 183) or excellent (39.1%, N = 124) by most physicians (Figure 2A). In particular, 86.4% (N = 274) and 62.7% (N = 199) of them reported a great/extreme improvement of symptoms in patients with acute and chronic diarrhea, respectively. A significant percentage observed such positive effects in their patients after only a few hours (35.0%, N = 111) or within 12 h (66.2%, N = 210).

The majority of physicians associated the use of Actitan-P with a good (64.4%, N = 204) or excellent (27.4%, N = 87) improvement in patient's quality of life (Figure 3A), and almost all (99.4%, N = 315) rated the safety and tolerability of the product as good or excellent (Figure 3B), with no interactions or side effects reported.

The clarity of the information on the package/insert regarding indications, instructions for use and warnings was rated as excellent or good by most physicians (>95%). The product was mainly prescribed as first-line treatment (83.6%, N = 265) or in combination with probiotics (60.3%, N = 191) (Figure 4C), with a recommended intake of two capsules twice daily (56.0%, N = 176) or three times daily (54.3%, N = 172).

In total, 331 physicians participated in the pediatric formulation survey (Actitan-F), including approximately two-thirds (63.1%, N = 209) of pediatricians. The product was prescribed to children aged 2 to 3 years (68.0%, N = 225), 4 to 6 years (67.4%, N = 223), 7 to 12 years (43.8%, N = 145) and 1-year-old children (44.1%, N = 146). Actitan-F was mainly prescribed for the treatment of acute diarrhea (i.e., due to suspected or proven viral infections [90.6%, N = 300] and associated with flu syndromes [73.4%, N = 243]), followed by functional chronic diarrhea (47.1%, N = 156) (Figure 1D).

A significant proportion of physicians reported that the beneficial effect occurred within a few hours (36.3%, N = 120) or within 12 h (65.0%, N = 215). Accordingly, the overall efficacy of the product was rated as good (53.3%, N = 177) or excellent (44.1%, N = 146) by the majority of participants (Figure 2B). In addition, 58.3% (N = 193) and 56.8% (N = 188) of physicians indicated that child caregivers found the product greatly/extremely easy to administer and greatly/extremely palatable, respectively.

Most physicians reported that the use of Actitan-F resulted in a good (57.4%, N = 190) or excellent (14.8%, N = 49) improvement in the child's quality of life (Figure 3C), and almost all respondents (98.8%, N = 327) rated the safety and tolerability of the product as good or excellent (Figure 3D), with no interactions or side effects reported.

The clarity of the information on the package/leaflet in terms of indications, directions for use and warnings was rated as excellent or good by the vast majority of physicians (>95% for each section of the package/leaflet). The product was mainly administered at a dosage of three sachets per day (48.9%, N = 162), followed by four sachets per day (42.9%, N = 142), two sachets per day (32.3%, N = 107) and one sachet per day (10.0%, N = 33). Most physicians prescribed Actitan-F as first-line treatment alone (85.2%, N = 282), followed by its use in combination with probiotics (55.6%, N = 184) and oral rehydration (51.1%, N = 169) (Figure 4D).

2.3. Pharmacists

In total, 550 pharmacists, 58.2% (N = 320) of whom work in independent private pharmacies, took part in the survey on the formulation for adults (Actitan-P). Almost all participants recommended the product for the treatment of acute diarrhea (99.5%, N = 547), and a significant proportion of them (65.1%, N = 358) also recommended it for the treatment of chronic diarrhea.

A significant proportion of pharmacists rated the efficacy of Actitan-P as good (52.9%, N = 291) or excellent (36.7%, N = 202) (Figure 2A). A significant percentage reported positive effects occurring within a few hours (33.5%, N = 184) or within 12 h (55.3%, N = 304).

Most pharmacists reported a good (58.5%, N = 322) or excellent (18.5%, N = 102) improvement in patient's quality of life as a result of taking Actitan-P (Figure 3A). Almost all respondents (97.6%, N = 537) rated the safety and tolerability of the product as good or excellent (Figure 3B), and no drug interactions or side effects were reported.

Most participants (>95% for each section) rated the clarity of the information on the pack/insert regarding indications, instructions for use and warnings as excellent or good. They mainly recommended Actitan-P as first-line treatment (79.1%, N = 435), in combination with probiotics (86.7%, N = 477) or oral rehydration (70.0%, N = 385) and as a substitute for loperamide (68.4%, N = 376) (Figure 4C). Consistent with the recommended dosages, most pharmacists recommended taking two capsules three times daily (80.5%, N = 443) or twice daily (30.9%, N = 170).

Regarding the pediatric formulation, 459 pharmacists completed the questionnaire, with 63.2% (N = 290) working in independent private pharmacies. The product was primarily recommended for the treatment of acute diarrhea (due to suspected viral infections [90.2%, N = 414] or associated with flu syndromes [91.7%, N = 421]) in children aged 2 to 3 years (33.4%, N = 350), 4 to 6 years (32.0%, N = 336), 7 to 12 years (14.3%, N = 150) and in 1-year-old children (19.1%, N = 200).

Most pharmacists rated the efficacy of Actitan-F as good (58.8%, N = 270) or excellent (35.5%, N = 163) (Figure 2B), with beneficial effects occurring within a few hours (21.9%,

N = 149) or within 12 h (43.8%, N = 298). In addition, 51.0% (N = 234) and 43.3% (N = 199) of respondents indicated that child caregivers found the product greatly/extremely easy to administer and greatly/extremely palatable, respectively.

A significant percentage of pharmacists reported that the use of Actitan-F resulted in a good (43.1%, N = 198) or excellent (8.1%, N = 37) improvement in the child's quality of life (Figure 3C), and almost all participants (97.9%, N = 449) rated the safety and tolerability of the product as good or excellent (Figure 3D), with no drug interactions or adverse effects reported.

The information on the package leaflet regarding the indications, directions for use and warnings of Actitan-F was rated as excellent or good by most pharmacists (>95%). Pharmacists generally recommended Actitan-F as first-line therapy (80.0%, N = 367) in combination with probiotics or oral rehydration (73.4% [N = 337] and 66.9% [N = 307], respectively) or as a substitute for loperamide (52.9%, N = 243) (Figure 4D).

3. Discussion

This study presents the results of two large surveys in which a total of 2,630 people from three different groups took part: patients/child caregivers, physicians and pharmacists. The main objective of this cross-sectional study was to collect clinical RWD on the perceived efficacy, safety, tolerability and pattern of use of Actitan. Actitan is a natural SBMD indicated for the treatment of adults (Actitan-P) and children (Actitan-F) with diarrhea. For this purpose, a newly validated, EU GDPR-compliant digital platform for clinical RWD collection was used [25]. This platform was implemented to properly handle the post-marketing surveillance and confirmation of the safety and performance of the product, including adverse events and benefit–risk assessments, as required by Regulation 2017/745 [20].

Overall, adult patients and child caregivers reported high levels of efficacy for both the adult and pediatric product formulations. In fact, most patients and child caregivers noted great/extreme improvements in diarrhea symptoms (75.5% and 82.8%, respectively) within a short period of time after using the products, ultimately leading to an improvement in quality of life. Remarkably, these positive perceptions were confirmed by the two groups of healthcare professionals (HCPs) involved.

Regarding Actitan's indications, the product was mainly prescribed by physicians and recommended by pharmacists for the treatment of acute diarrhea, although a non-negligible proportion of HCPs recommended the product for chronic conditions, such as functional diarrhea (21.8% and 47.1% for adult and pediatric formulation, respectively), and inflammatory bowel disease in adults (15.8%). This observation is consistent with the information provided by patients/caregivers who primarily used the product for acute conditions. Regardless of the strong tendency to self-medicate, this agreement probably reflects the higher incidence of acute diarrhea and the low willingness to seek medical attention for acute illnesses due to their rapid onset and distressing symptoms [26,27]. Interestingly, the tendency to self-medicate was lower for the pediatric product (63%) than for the adult formulation (85%), possibly indicating a greater willingness to seek medical attention when a child is affected.

Nevertheless, the collected data indicated a high level of compliance with Actitan's indications and dosage, as reported on its packaging and leaflet. The clarity of this information was favorably evaluated by the vast majority of participants, which may explain the good levels of adherence observed both in patients/caregivers and healthcare professionals.

An earlier study by Russo et al. [24] already investigated the clinical efficacy, safety and compliance of Actitan-F when used as an add-on therapy to standard oral rehydration (SOR) in 60 children (aged between 0.3 months and 12 years) with acute gastroenteritis and non-severe dehydration. In the Actitan-F group, a significant change ($p < 0.0001$) was observed in the number of stools between the baseline and 24 h after treatment. In terms of stool consistency, the percentage of patients with formed stools (according to the Bristol

Stool Form Scale) on the sixth day of treatment was significantly higher in the Actitan-F group than in the SOR-only group (76.9% vs. 50%; $p = 0.028$).

In all cohorts, both the adult and pediatric formulations were found to be very safe and well tolerated (>90% in all cohorts), which is a clinically relevant finding in the context of diarrhea treatment. Although various medications can effectively treat both acute and chronic diarrhea, their use at any age is associated with some disadvantages. Antibiotic therapy for acute diarrhea, which is rarely caused by bacterial or parasitic infections, is generally considered unnecessary [15,16] and may have unhealthy effects on the gut microbiota [17,18]. In some cases, e.g., enterohemorrhagic *Escherichia coli* infection [19], it may even be counterproductive. According to the guidelines of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), probiotics with proven efficacy, such as *Saccharomyces boulardii* and *Lactobacillus rhamnosus GG*, can be considered adjunctive therapy for acute diarrhea [28,29]. While the level of recommendation is very high, the quality of the evidence is low. Opiate antidiarrheals are often used as empirical therapy but are not recommended for infants. Furthermore, they should be administered to young children under medical supervision, as they are not free of side effects and are generally not recommended for prolonged use.

In this context, there is growing interest in the use and development of substance-based medical devices as therapeutic options [30,31]. In a randomized, cross-over clinical trial, a substance-based medical device containing xyloglucan, which acts as a mucosal protector, was shown to be effective in treating diarrhea-predominant irritable bowel syndrome [32]. This further highlights the validity of a non-pharmacological therapeutic approach based on the protection and strengthening of the intestinal barrier for the treatment of diarrhea and other intestinal disorders [33].

When asked about the most common age group of pediatric patients treated with Actitan-F, over 44% of doctors surveyed cited the one-year-old category. As already mentioned, this group is a special subgroup of children for whom treatments with a favorable risk–benefit profile are only available to a very limited extent [34,35]. Furthermore, except for one case of constipation in an adult patient, no potentially related adverse effects or interactions with other concomitant treatments were reported, providing further evidence that there are no safety issues.

Overall, Actitan appears to meet the basic criteria of an effective antidiarrheal agent, namely, a high safety profile allowing use without close specialist supervision; compatibility with other complementary therapeutic options; and efficacy in treating both acute and chronic diarrhea of any cause, all at a moderate cost. It should be noted that the RWD collected here are valuable for estimating the magnitude of clinical benefit and safety in the general population and thus provide a fairly accurate overall assessment of the benefit-risk profile of the treatment. In addition, both the adult and pediatric formulations are 100% natural products and, therefore, by definition, biodegradable and have no impact on the environment [36].

The design and method of data collection had some limitations: participants were partially self-selected and were not unbiased, as internet access and basic internet skills were required to participate in the digital survey. In addition, patients' quality of life was assessed using a limited number of parameters; for Actitan-P, participants were asked to rate improvements in mood, social life, work, eating freely, exercise and freedom to travel, while for Actitan-F, participants were asked to rate improvements in mood, crying, eating, ability to play and sleep in their children. These short versions were preferred to the validated quality of life questionnaires, which usually contain at least 15 questions, to avoid low completion rates due to the large number of items. Finally, since they were collected through real-world surveys, the data presented here should be interpreted as reflecting the perspectives of users, including both patients and healthcare professionals.

In summary, the present RW data collection shows that Actitan-P and Actitan-F are highly effective and safe in the treatment of diarrhea in adults and children, respectively. Patients and healthcare professionals reported significant improvements in symptoms and

quality of life, as well as high levels of safety and tolerability. These results support Actitan as a valid option for the treatment of diarrhea of any cause and in different age groups, including very young children.

4. Materials and Methods

4.1. Product

The product under evaluation, Actitan, is available in both an adult formulation and a pediatric formulation. The adult formulation contains Actitan-P, a complex herbal system containing a mixture of tannins from agrimony and tormentil and polyphenols from olive and turmeric. The pediatric formulation consists of sachets of Actitan-F, another complex herbal system containing tannins from agrimony and tormentil and flavonoids from chamomile. Adults are recommended to take 2 capsules 2–3 times a day depending on the severity of the condition, while for children, the recommended dosage is 1 sachet every 3 h up to a maximum of 4 sachets per day, also depending on the severity of the condition [21,22].

4.2. Study Design

To evaluate the efficacy and safety profiles of Actitan-P and Actitan-F, two observational studies were conducted with three different cohorts: patients/caregivers, physicians and pharmacists. All clinical RWD were collected via a structured GxP web platform [25]. Patients could access the platform via a website link or a QR code provided on the product packaging. The purchase is verified by entering a batch number and a unique code, both found on the package, before beginning the online questionnaire. Similarly, physicians and pharmacists can access the platform via a dedicated healthcare professionals' section on the manufacturer's website, on their own initiative. Additionally, physicians were directly recruited by the manufacturer's scientific representatives [25]. The Actitan-P survey was conducted from 1 September 2021 to 26 September 26 2022, and the Actitan-F survey took place between 1 September 2021 and 5 October 2022. The clinical data were collected using digital questionnaires developed by clinical experts in collaboration with the Department of Biomedicine, Surgery and Dentistry at the College of Milan. These questionnaires were specifically tailored to the groups of people surveyed and covered various aspects such as efficacy, dose adherence, quality of life, possible side effects and misuse. Patients were asked to share their experiences with the device, while physicians and pharmacists were asked about their patients' experiences. This approach allowed for the indirect validation of the data reported by patients. To assess the level of accuracy of the current survey, a repeatability study was conducted before the questionnaires were sent to participants. This preliminary study also served as an indirect measure of the potential validity of the questionnaire [26]. The repeatability study was conducted for a different product than Actitan, but the methodology and question structure were identical. Therefore, it is reasonable to consider the repeatability of the results as relevant to current surveys.

4.3. Personal Data

Due to the non-anonymous nature of the data, information was provided to each participant as of 2018 in accordance with Italian laws and regulations on the protection and management of personal data and the EU General Data Protection Regulation (GDPR). Each participant declared to have read and accepted this information.

4.4. Sample Size and Statistical Analysis

Patient/caregiver sample size calculations resulted in a minimum population of 583 respondents for Actitan-P and a minimum sample size of 318 respondents for Actitan-F. These calculations included questions on efficacy, safety, tolerability, quality of life and symptom improvement. The assumptions included a margin of error of 4%, a 95% confidence level, and an estimated response rate of 50% for Actitan-P (a conservative estimate) and a margin of error of 5%, a 95% confidence level, and an estimated response rate of 70%

for Actitan-F (based on previous questionnaire results). The calculations were performed using an online tool available at http://www.raosoft.com/samplesize.html (accessed on 5 December 2022).

Descriptive analyses were performed for each question, with results reported in absolute numbers and percentages. For both single and multiple-response questions, the percentage corresponds to the proportion of respondents who chose that response unless otherwise stated.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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