

Acceptability, tolerability, and effects on symptoms and signs of vulvovaginitis of a non-soap, herbal-based intimate hygiene solution (Zelesse®)

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Abstract

Objective: To evaluate the acceptability, tolerability, and effects on vulvovaginitis symptoms and signs of a non-soap, herbal-based intimate solution (Zelesse®).

Methods: We conducted a prospective, observational, multicenter study including adult women with symptoms and signs of vulvovaginitis with various etiologies, including candidiasis, trichomoniasis, bacterial vaginosis, and atrophic and irritative vaginitis. The presence and intensity of signs (edema, erythema, vaginal discharge) and symptoms (pruritus) of vulvovaginitis were evaluated before and after 5–15 days of daily use of Zelesse® alone or as a coadjuvant in antimicrobial therapy. Variables following a normal distribution and categorical variables were analyzed using the Student t-test and chi-square or Fisher's exact test, respectively.

Results: A total 137 women were enrolled in the study; 87 (63.5%) women received concomitant antimicrobials and 50 (36.5%) used Zelesse® only. Global symptom scores and frequency of patients with vulvovaginitis signs and symptoms, and their mean intensity, decreased after treatment in both patient groups. Vaginal pH and (in the Zelesse®-only group) vaginal flora remained unaltered. The product was safe, well tolerated, and highly accepted by patients.

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Conclusions: Zelesse[®], the non-soap herbal-based solution in this study, may represent a safe and effective option for symptomatic relief of vulvovaginitis.

Keywords

Vulvovaginitis, pruritus, aloe vera, intimate hygiene, burdock, chamomile

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Introduction

Vulvovaginitis is the general term for disorders of the vulva, vagina or both, caused by infection, inflammation, or changes in the normal vaginal flora. The main symptoms include pruritus, burning, odor, and vaginal discharge, accompanied by signs of vulvar irritation and inflammation, such as erythema or edema. Vulvovaginal disorders are among the most common reasons for which women seek the advice of a gynecologist.¹ The most common causes of vulvovaginitis include bacterial vaginosis, which is produced by a microbial imbalance in the vaginal flora that can ultimately lead to negative health consequences; vulvovaginal candidiasis; and trichomoniasis.²⁻⁴ Other causes include cytolytic vaginosis, aerobic vaginitis, and unspecific processes related to irritant or allergic contact dermatitis, foreign bodies, or atrophic vaginitis.³⁻⁵ Current recommendations for women with symptomatic disease include antimicrobial therapy to relieve vaginal symptoms when an infectious origin is suspected.^{1,2,6} Despite a suggested potential benefit of appropriate feminine hygiene products for the symptomatic relief of vulvovaginitis,^{7,8} studies assessing the effects of these on the symptoms and signs of vulvovaginitis are scarce.

Zelesse[®] (ITF Research Pharma S.L.U., Alcobendas, Madrid, Spain) is an active, non-soap, intimate care solution based on

burdock (*Arctium majus*), chamomile (*Chamomilla recutita*), and aloe (*Aloe barbadensis*). Zelesse[®] has been marketed in Europe since 2013, according to healthcare products regulations. The herbal components (burdock, chamomile, and aloe vera) of Zelesse[®] are natural ingredients known for their anti-inflammatory, anti-allergic, and anti-oxidant properties and are widely used in dermatological disorders⁹⁻¹⁵ given their soothing, antipruritic, and antiseptic properties. Therefore, this solution may exert favorable effects in the management of vulvovaginitis, although, to date, there is no clinical evidence reported in this regard. The aim of this study was to evaluate the effect, tolerability, and acceptability of Zelesse[®], used either alone or in combination with specific pharmacological treatment, for relief of the symptoms and signs of vulvovaginitis.

Patients and methods

Study design and population

This was a prospective observational multicenter study, including adult women (age >18 years) who attended outpatient gynecology offices in Spain for concerns about the symptoms and signs of vulvovaginitis and for whom their gynecologist recommended daily genital washing with Zelesse[®] to alleviate these signs/symptoms, in the setting of routine clinical practice.

The presence of vulvovaginitis was determined by assessing the patient's symptoms and signs (including vaginal pH measurement and microscopic examination of a vaginal discharge sample), and following the assessment criteria used in routine practice at each site. Likewise, regular vaginal washes with Zelesse® were recommended at each physician's discretion, according to regular clinical practice. Exclusion criteria were pregnancy, contraindications for the use of intimate wash products, and known hypersensitivity to any of the solution ingredients. Study participants signed an informed consent form prior to study inclusion. The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Universidad Católica de San Antonio, Murcia, Spain.

Intervention and assessments

Patients included in the study underwent visits at baseline and at the end of treatment, and were asked to perform daily (either once or twice a day) genital washing with Zelesse® during a period ranging between 5 and 15 days. Oral or topical antimicrobial therapy was permitted when indicated by the physician. Patients' demographic and clinical characteristics, including age and predisposing factors, were recorded at the initial visit. Other variables considered in this study were assessed at the initial and final visits, including the presence and intensity of symptoms and signs of vulvovaginitis (visual genital exam) and vaginal pH; a vaginal discharge sample was also collected for subsequent analysis. Based on the variables obtained at the initial visit and the clinical criteria supported by the results of wet mount microscopy, gynecologists differentially diagnosed vulvovaginitis (infectious vs. noninfectious) and recommended the use of Zelesse® alone or in combination with antimicrobial

treatment, as appropriate. Gynecologists at the study sites scored the intensity of vulvovaginitis signs and symptoms as follows: 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). A composite score (Global Score) comprising the sum of all individual scores was calculated to estimate the effect of treatment on the global symptomatology and manifestations of vulvovaginitis (score range 0–12). To assess safety and tolerability, participants were encouraged to spontaneously report, and gynecologists to proactively ask, about any adverse events occurring during treatment. Patients were also asked to rate global tolerability as "excellent", "very good", "good", "or "poor". Acceptability was assessed by asking participants to choose the most notable properties of the product from among the following options: "refreshing", "soothing", "nice smell", and "ease or comfort of use". Patients' assessment was based on self-perception of their clinical evolution, rated as "cured", "much improvement", "slight improvement", "no change", or "worsening". Patients were also asked about the number of days elapsed before self-perception of improvement.

Statistical analysis

All evaluable patients were included in the analysis. Analyses were performed using descriptive statistical methods. Continuous variables were described as the number of patients with valid or missing observations, mean and standard deviation (SD). Categorical variables were described with absolute and relative frequencies. Variables following a normal distribution were evaluated using the Student t-test. For categorical variables, the chi-square or Fisher's exact test were applied, as necessary. The significance level was set at a p value <0.05.

Results

Clinical and treatment characteristics of the study participants

Of the 137 women enrolled, 96.3% were white and 3.7% Hispanic; all participants completed the study. The mean (SD) age of patients was 38.7 (11.2) years. The prevalence of predisposing factors for vulvovaginitis were use of antibiotics (18.2%), oral contraceptives (17.5%), estrogen-deprivation drugs (1.5%), corticosteroids (2.9%), use of an intrauterine device (IUD) or vaginal ring (13.9%), inadequate hygiene (14.6%), use of tight or synthetic underwear (18.2%), and use of panty liners (21.2%), among other factors. Eighty-seven (63.5%) women were treated with a specific antimicrobial drug apart from the study product (group with antimicrobial treatment), and 50 (36.5%) women received no concomitant antimicrobials (Zelesse[®] only group or

group without antimicrobial treatment). Table 1 summarizes the baseline clinical characteristics of participants, which were similar between both groups, as well as the characteristics of vaginal flora. In 56.9% of patients, the episode under study was the first episode of vulvovaginitis, which was more frequent in the group without antimicrobial treatment than in the group with antimicrobial treatment (72% and 48.3%, respectively; $p=0.007$). At baseline, the most frequent symptom was pruritus (93%), followed by erythema (80%), vaginal discharge (75%), and edema (59%), shown in Figure 1 for each study group. The intensity of all symptoms and signs was rated, on average, as mild to moderate. Pruritus was the most intense complaint expressed by patients, followed by edema.

Regarding the use of the study product, 89.3% of women used Zelesse[®] once or

Table 1. Baseline characteristics of study patients according to treatment

	n ^a	With antimicrobial treatment n=87	Without antimicrobial treatment n=50	Total n=137
Clinical characteristics, n (%)				
Symptoms and signs of vulvovaginitis	137			
Pruritus		85 (98)	43 (86)	128 (93)
Erythema		75 (86)	34 (68)	109 (80)
Edema		57 (65)	24 (48)	81 (59)
Vaginal discharge		72 (83)	31 (62)	103 (75)
pH, mean (SD)	121	5.31 (0.99)	5.47 (0.94)	5.37 (0.97)
Vaginal flora	113			
Normal, n (%)		13 (17.1)	26 (70.3)	39 (34.5)
Altered ^b , n (%)		3 (3.9)	1 (2.7)	4 (3.5)
<i>Candida</i> , n (%)		38 (50.0)	7 (18.9)	45 (39.8)
<i>Gardnerella</i> ^c , n (%)		11 (14.5)	2 (5.4)	13 (11.5)
<i>Trichomonas</i> , n (%)		1 (1.3)	0 (0)	1 (0.9)
<i>E.coli</i> / <i>Streptococcus</i> / <i>Enterococcus</i> , n (%)		2 (2.6)	1 (2.7)	3 (2.7)
<i>Candida</i> and <i>Gardnerella</i> , n (%)		1 (1.3)	0 (0)	1 (0.9)
<i>Candida</i> and <i>Trichomonas</i> , n (%)		1 (1.3)	0 (0)	1 (0.9)
Other, n (%)		6 (7.9)	0 (0)	6 (5.3)

^aNumber of evaluable patients (none missing).

^bReferred to as such in the case record form.

^cAccording to evidence of clue cells.

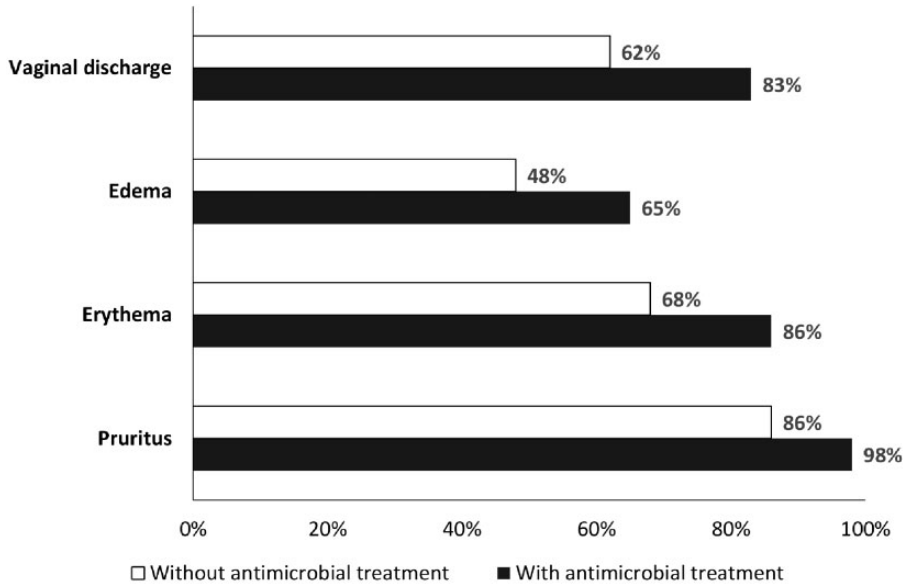


Figure 1. Distribution of vulvovaginal manifestations at baseline in both groups (with and without antimicrobial treatment)

twice daily, according to their gynecologist's indications. Twice daily application was higher in the group treated with antimicrobial drugs (64.4% vs. 49.0%; $p = 0.024$). Mean (SD) duration of treatment with Zelesse[®] was 12.4 (7.1) days, and mean (SD) time before clinical improvement was 3.4 (2.7) days, with no differences between groups.

Treatment efficacy and safety

All clinical manifestations of vulvovaginitis were significantly improved by the end of the treatment. Changes in the intensity of clinical manifestations between the baseline and final visit (after treatment) for the two study groups are shown in Figure 2. In the group treated with Zelesse[®] only, pruritus improved in 93% of women. At the final visit, pruritus was mild or had disappeared in 94% of women. Erythema improved in 70% of women, and 96% had mild or no erythema after treatment. Regarding

edema, 87% of women noticed improvement, and 98% had mild or no edema after treatment. Finally, the degree of vaginal discharge improved in 77% of women, and 90% had mild or no vaginal discharge after treatment. On the other hand, in the group that used Zelesse[®] together with antimicrobial treatment, 91% of women either had no pruritus or it was present to only a mild degree after treatment; 96% had mild or no erythema, 97% had mild or no edema, and 92% had mild or no vaginal discharge after treatment.

After treatment, the Global Score was significantly decreased in both groups, from 4.9 to 1.5 in the Zelesse only group and from 7.4 to 1.4 in the group that received combined treatment ($p < 0.001$, Wilcoxon test, for both comparisons) (Figure 3).

There were no significant differences in vaginal pH before and after treatment (5.31 vs. 5.37 in the group with antimicrobial therapy; 5.47 vs. 5.47 in the group

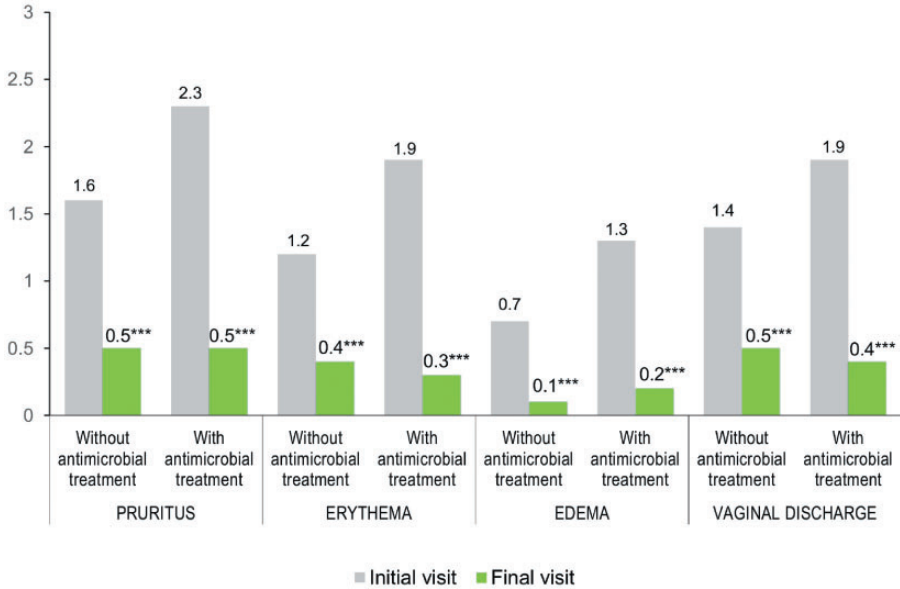


Figure 2. Intensity of vulvovaginal manifestations at baseline and after treatment in groups with and without antimicrobial treatment. *** $p < 0.0001$, compared with baseline

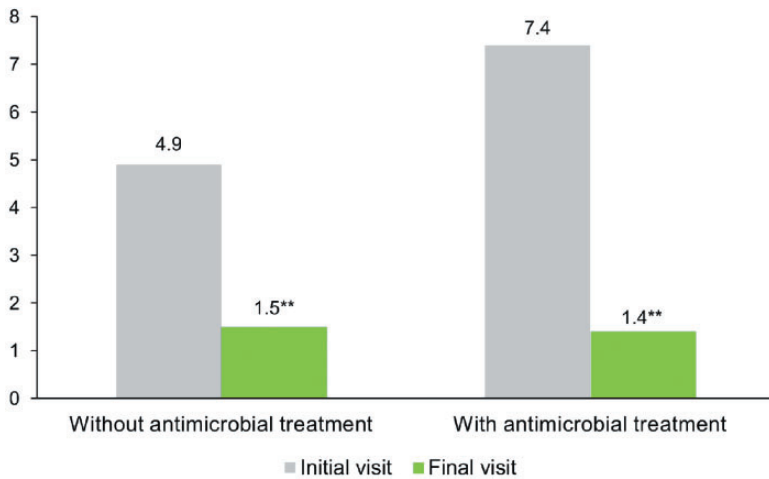


Figure 3. Change in the global symptoms score (range 0–12) from baseline to final visit in groups with and without antimicrobial treatment. ** $p < 0.001$

without antimicrobial treatment). Regarding vaginal flora, in the group with antimicrobial therapy, 50% (38/76) of women demonstrated *Candida* spp. and 14.5% (11/76) had clue cells in vaginal

smears, suggestive of *Gardnerella* at baseline. At the end of treatment, 90% (30/33) of women in the group with antimicrobial treatment had normal vaginal flora. In the group without antimicrobial treatment,

70.3% (26/37) of women had normal vaginal flora at baseline. Only 10 women in the group without antimicrobial treatment had a vaginal discharge sample analyzed at baseline and after treatment, among which 7 showed normal vaginal flora in both analyses, 2 women had persistent evidence of *Candida* and *Escherichia coli*/*Streptococcus*, and 1 woman had previous evidence of *Candida* and later showed normalized flora.

Of four adverse events recorded, three were related to the study product (one report of severe vulvovaginal pruritus, one of mild burning, and one of mild discomfort). All events resolved and no additional measures were required.

Treatment efficacy in postmenopausal women

Of the 137 women included in the study, 22 were postmenopausal. Eleven of them (aged 59.9 ± 6.5 years) had nonspecific vulvovaginitis whereas the remaining 11 women (aged 52 ± 7.8 years) had symptoms and signs of vulvovaginal infection. At baseline, 20 women (91%) had pruritus, 19 (86%) had erythema, 14 (63%) had edema, and 9 (41%) had vaginal discharge. After treatment, 19 women (95%) had improved pruritus, 16 (84%) improved erythema, 14 (100%) improved edema, and 8 (89%) women had improved vaginal discharge. Additionally, in the groups with and without antimicrobial treatment, the intensity of pruritus decreased from 1.8 to 0.6 ($p=0.007$) and from 2.4 to 0.8 ($p=0.01$); that of erythema dropped from 1.8 to 1.0 ($p=0.04$) and from 2.3 to 0.4 ($p=0.007$); that of edema decreased from 1.8 to 0.1 ($p=0.04$) and from 2.0 to 0.2 ($p=0.01$); and the intensity of vaginal discharge declined from 2.5 to 1.0 ($p=0.06$) and from 2.2 to 1.0 ($p=0.06$), respectively (Figure 4). The Global Score showed a significant improvement in both groups among postmenopausal women, from

5.1 to 1.8 ($p=0.005$; Wilcoxon Test) in the group without antimicrobial treatment and from 7.0 to 1.8 ($p=0.005$; Wilcoxon Test) in the group with antimicrobial treatment (Figure 5).

Patients' and gynecologists' perceptions of treatment efficacy

Regarding patients' self-perception of clinical evolution, 77.1% and 83.9% of women in the groups without and with antimicrobial treatment, respectively, perceived that Zelesse[®] contributed to curing or greatly improving their vulvovaginal manifestations. The properties most frequently noted by patients were the product's soothing effect (62.0%), refreshing action (51.8%), nice smell (40.9%), and ease of use (35.8%); 84.6% patients rated the tolerability of Zelesse[®] as excellent or very good.

Discussion

In this prospective, observational study among 137 women with vulvovaginitis of different etiologies, the results showed that a short treatment regime of daily intimate washing with Zelesse[®] alone, or as a co-adjuvant in antimicrobial therapy, was safe and effective in improving the signs and symptoms of vulvovaginitis, i.e., pruritus, erythema, edema, and vaginal discharge. The product was very well tolerated by patients, and both patients and gynecologists considered that the treatment had contributed to the improvement of vulvovaginal manifestations.

The results obtained suggest that Zelesse[®] is an effective measure for the relief of characteristic symptoms of acute nonspecific vulvovaginitis when there is no suggestion of an infectious etiology. Zelesse[®] may also be useful for relieving the symptoms of infectious vulvovaginitis when specific treatment may be delayed by

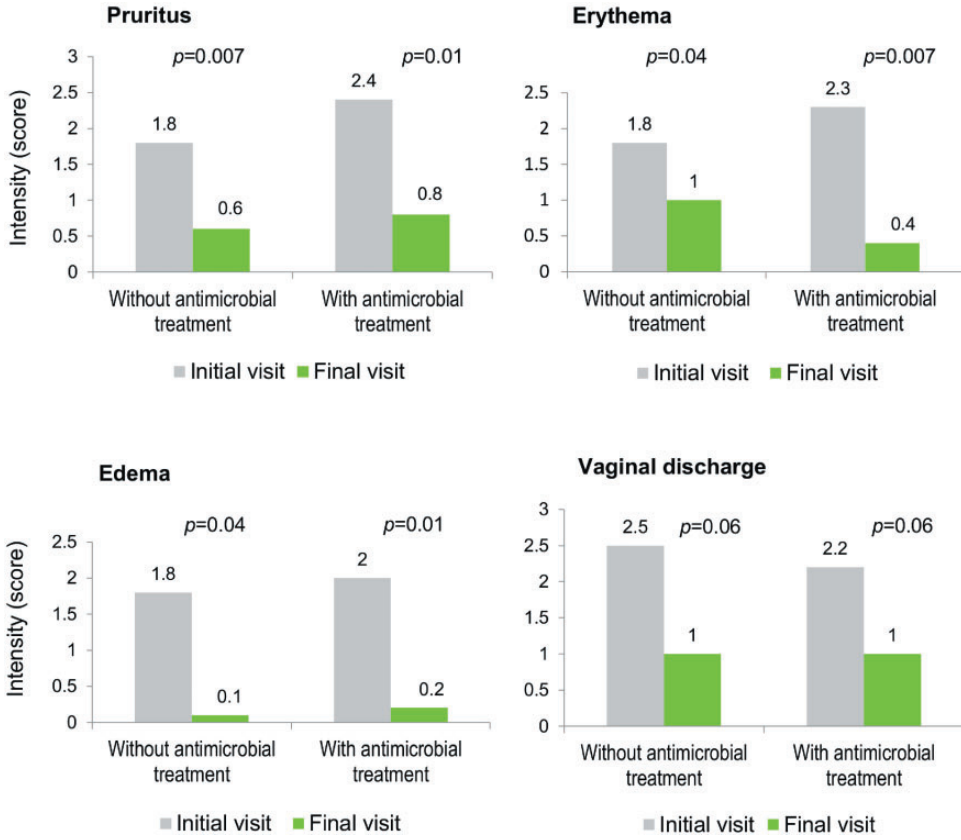


Figure 4. Reduction in the intensity of symptoms (range 0–3) from baseline to final visit in postmenopausal women with and without antimicrobial treatment

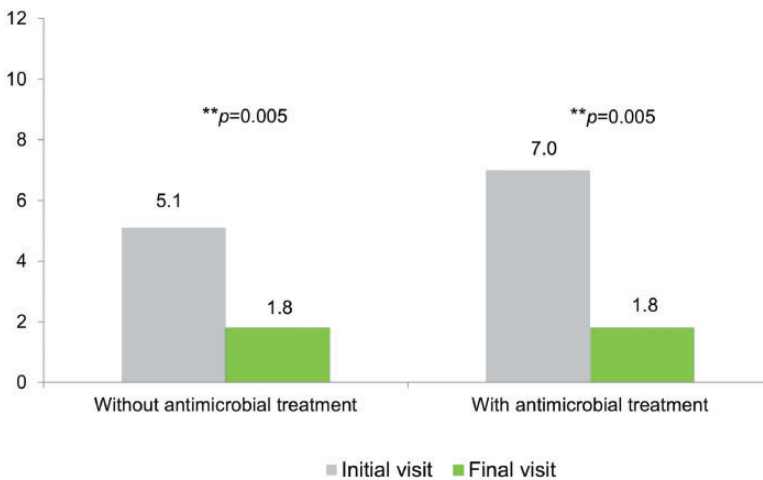


Figure 5. Change in the global symptoms score (range 0–12) from baseline to final visit in postmenopausal women with and without antimicrobial treatment ****p < 0.005**

the absence of a definitive microbiological diagnosis.

Zelesse[®] was particularly effective against pruritus, which is the most relevant and troublesome symptom experienced by patients and the most common reason why patients consult a doctor, as pruritus usually does not disappear spontaneously and must be managed with symptomatic treatment.¹⁶ In this study, we found that this symptom was the most commonly cited complaint at the initial visit, mentioned by 94% of women. In the group that only received symptomatic treatment with Zelesse[®], pruritus improved in 93% of women (40 of 43), as the intensity of the symptom declined or the pruritus disappeared. It is noteworthy that 31 women (62%) presented with moderate or severe pruritus at the baseline visit, and only 3 (6%) of them experienced moderate or severe pruritus at the final visit. Furthermore, at the final visit, pruritus was absent or only mildly present in the vast majority (94%) of women in the group that did not receive antimicrobial treatment. Zelesse[®] had also a clear beneficial effect on other manifestations of vulvovaginitis, improving erythema, edema, and vaginal discharge in 70%, 87%, and 77% of patients, respectively. In addition, erythema, edema, and vaginal discharge were absent or reduced to mild intensity in most women (94%, 96%, and 84%, respectively) after treatment. Following administration of Zelesse[®], the mean change in intensity of signs and symptoms was of more than one degree and, overall, the intensity decreased to a level of less than mild in all cases.

We also queried patients' opinions regarding the overall easing of their vaginal discomfort; which are particularly interesting from a clinical point of view, as women are often unable to define, specify, or grade the distinct symptoms and signs. In the group of women without antimicrobial

treatment, three of every four considered that treatment with Zelesse[®] had improved or resolved their discomfort, which agreed with the researchers' assessment regarding the contribution of this product to improving the patients' condition. Importantly, this result matches the effect of Zelesse[®] in improving the global symptomatology in these women, as demonstrated by the significant improvement in the Global Score. Nevertheless, the fact that global scores, and the prevalence and intensities of symptoms and signs decreased in the absence of pharmacological treatment, suggests a beneficial effect in this group of patients. The most noted quality of Zelesse[®] was its soothing action, which relates to the main properties of its components, and explains its beneficial effect on symptoms.

Zelesse[®] was evaluated as an adjuvant in women with vulvovaginitis of suspected infectious etiology, who received that solution plus specific treatment (group with antimicrobials). Given that the effects in this group could only be attributed to the combination of treatments, it was not possible to evaluate the efficacy of Zelesse[®] in resolving symptoms; however, it was possible to analyze the tolerability and acceptability of the product in these women. Results confirmed that Zelesse[®] is a well-tolerated option in women with vulvovaginitis. In this sense, the great majority of patients (85%) stated that the tolerability of Zelesse[®] was excellent or very good and there were only four episodes of mild adverse events, possibly not related to application of the product. In addition, the solution maintained the balance of the vaginal flora and the pH, an important characteristic as any alteration could favor colonization by opportunistic pathogens and predispose the patient to infections or, if applicable, superinfections.

In this study, the results of the overall evaluation of signs and symptoms in both groups of women is notable. Women in the

group that received Zelesse[®] plus antimicrobial treatment initially presented with more intense symptoms than women in the group without antimicrobial treatment (mean global symptom scores of 7.4 and 4.8, respectively). However, after treatment, the global symptom scores were similar for both groups (1.4 and 1.5, respectively), which again points to the beneficial effects of Zelesse[®] in this pathology.

The results from this study should be interpreted in the context of certain limitations. As an observational study, Zelesse[®] was recommended in the setting of routine practice; hence, the criteria for initiating vaginal washes were at the physician's discretion and could not be predetermined and standardized in the study protocol. In this regard, the description of the clinical characteristics presented in the results section is of special relevance for defining the scope of the effectiveness results. In line with the observational design, the lack of a placebo treatment precludes direct comparisons with no treatment; instead, the effect of Zelesse[®] was assessed by comparing the frequency and intensity of symptoms and signs of vulvovaginitis before and after treatment. Whereas signs of vulvovaginitis (i.e., vaginal discharge, edema) were assessed by a physician and therefore were not influenced by a placebo effect, the possible contribution of a placebo effect to the improvement of symptoms cannot be ruled out. Furthermore, vulvovaginitis was considered as a whole, precluding the detection of differential effects of Zelesse[®] according to different etiologies; it would be interesting to analyze signs and symptoms according to specific diagnoses in future studies. An additional limitation is the absence of a follow-up visit, which might have provided interesting information regarding potential symptom relapse among participants. Despite these limitations, the main strength of this study is that, to our knowledge, this is the first

clinical study addressing the potential effects on vulvovaginitis of a non-pharmacological intimate solution product in a real-world setting.

In conclusion, the results from this study show that Zelesse[®] is highly effective in treating the symptoms and signs of both nonspecific and infectious vulvovaginitis among adult women. Regardless of the beneficial effects of Zelesse[®] for vulvovaginitis symptoms and signs, a proper diagnosis should be established to ensure that the appropriate treatment is prescribed. Zelesse[®] is particularly effective for relieving itching, the most troublesome symptom of acute vulvovaginitis. Our results provide clinical evidence that Zelesse[®] is very well tolerated and does not alter the vaginal ecosystem. Thus, after a proper diagnosis is made, Zelesse[®] may be a beneficial option for the management of symptoms and signs of vulvovaginitis with different etiologies.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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