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Efficacy, acceptability and tolerability of Zelesse® for the treatment of non-specific vulvovaginitis in paediatric patients: The NINESSE Study

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Abstract

Objective: To evaluate the efficacy, tolerability and acceptability of Zelesse®, an intimate hygiene wash solution, in the relief of the symptoms and signs of non-specific vulvovaginitis in paediatric patients.

Methods: The NINESSE Study was a prospective, observational, multicentre study involving females aged 2–8 years who attended paediatric offices with symptoms suggestive of non-specific vulvovaginitis. They were administered Zelesse® as a single treatment for 15 ± 5 days. Pruritus, burning, dysuria, erythema, leucorrhoea and oedema were evaluated before and after treatment.

Results: A total of 71 paediatric patients were enrolled in the study (mean $\pm$ SD age, 4.5 ± 1.9 years). The most significant effects were observed for pruritus and burning, where 98.4% (62 of 63) and 96.9% (63 of 65) of the patients improved after treatment, respectively. Zelesse® demonstrated a beneficial effect on dysuria, erythema, leucorrhoea and oedema. The effects on the symptoms and signs were observed within the first week of treatment; although 44.9% (31 of 69)

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of patients experienced improvements after 2–3 days. Zelesse® was well accepted and tolerated by most patients. No serious adverse events were reported.
Conclusions: Zelesse® was very effective for the relief of the symptoms and signs of non-specific vulvovaginitis, in particular pruritus, burning and erythema, in females aged 2–8 years.

Keywords
Acceptability, efficacy, non-specific vulvovaginitis, paediatric, tolerability, Zelesse®

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Introduction

Vulvovaginitis, which is inflammation of the vulvar and vaginal areas, is the most frequent gynaecological condition occurring in prepubertal girls.[1,2] It is caused by either a pathogenic infection (including intestinal parasites, respiratory streptococci and *Candida spp*.) or by a non-specific aetiology, such as trauma, dermatological conditions or congenital disorders.[3,4] The prevalence of non-specific vulvovaginitis ranges between 25% and 75% of cases in prepubertal girls.[1,5,6] The most common symptoms and signs include pruritus, burning, dysuria, erythema, leucorrhoea and oedema.[3,7] Interestingly, a high percentage of non-specific vulvovaginitis cases are recurrent.[7] The diagnosis is clinical and is mainly based on an adequate anamnesis and physical examination.[8] Factors associated with the risk of vulvovaginitis include a hypoestrogenized vaginal mucosa, lack of development of the labia minora, close proximity of the vagina to the anus, poor hygiene, tight-fitting clothing or the use of shampoos or soaps.[7,9,10] Some hygienic sanitary measures are fundamental in the management of non-specific vulvovaginitis, such as avoiding wet clothing (in contact with the genital area) for long periods and avoiding the use of tight-fitting and synthetic clothing.[9] While the use of cotton underwear and adequate cleansing of the body with warm water and soap, excluding the genital area, are recommended.[9] Symptoms of non-specific vulvovaginitis can also be adequately controlled with the use of topical products.[11] In this context, Zelesse® (ITF Research Pharma S. L.U., Madrid, Spain) is an intimate hygiene wash solution based on chamomile, burdock and aloe vera, marketed since 2013,[11] which is beneficial for the management of non-specific vulvovaginitis in adult women. An observational multicentre clinical study of 50 adult women with non-specific vulvovaginitis (or presumably with no infectious origin) who used Zelesse® once or twice daily for 15 days demonstrated that all symptoms and signs associated with vulvovaginitis improved significantly after treatment.[12] A total of 93% of women showed improvement in pruritus, 87% in oedema, 77% in leucorrhoea and 68% in erythema.[12] Pruritus, leucorrhoea and erythema were cured in 53%, 42% and 44% of women, respectively.[12] Moreover, 82% of women considered the tolerability of the product to be very good or excellent; and highlighted its soothing and refreshing properties.[12] Improvement of symptoms and signs after the treatment with Zelesse® was also demonstrated in the study, which included 50 women with symptoms of non-specific vulvovaginitis

and 87 women with vulvovaginal infection.[12,13] Among women with non-specific vulvovaginitis, 93% of those with pruritus at baseline reduced its intensity from 1.9 to 0.5 after the treatment.[12] Zelesse® also improved erythema, oedema and vaginal discharge.[14] Similarly, Zelesse® decreased the Global Symptoms and Signs (GSS) score of women with non-specific vulvovaginitis from 4.8 at baseline to 1.5 after treatment.[15]

Given the prevalence of non-specific vulvovaginitis in the prepubertal population and the absence of investigations of Zelesse® in children, this present study aimed to investigate the use of Zelesse® in a cohort of female patients aged between 2 and 8 years. The main objectives of the study were to evaluate the efficacy, tolerability and acceptability of Zelesse® in the relief of symptoms and signs of non-specific vulvovaginitis in paediatric patients.

Patients and methods

Study design

The NINESSE Study was a prospective, observational, descriptive, multicentre study involving female paediatric patients aged 2 to 8 years attending a paediatric office with symptoms and signs suggestive of non-specific vulvovaginitis and whose paediatrician considered that hygienic measures could be beneficial for their condition. The inclusion of the patients was consecutive upon their arrival to the paediatric office. The clinical study was performed between March 2016 and May 2016. The study was carried out in 13 private and public paediatric centres located in Madrid, Barcelona, Ourense, Pontevedra and A Coruña. Exclusion criteria were: (i) vulvovaginitis with specific aetiology, such as caused by pathogens, congenital abnormalities and traumas; (ii) any disorder or characteristic in girls that, according to the investigator's opinion, could interfere with the study results; (iii) having experienced the menarche; (iv) hypersensitivity to any component of Zelesse®; (v) concomitant participation in another clinical study. All patients received treatment with Zelesse® for 15 ± 5 days in a dose of 3–5 ml, once, once or twice (as needed), or twice daily according to investigator's decision. The study required two visits to the paediatrician: one at baseline and another one after treatment.

All procedures were undertaken in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain. All parents or legal guardians signed the written informed consent to participate in the study.

Endpoints and variables

The study endpoints were designed to evaluate the efficacy, tolerability and acceptability of Zelesse® in this population of paediatric patients with non-specific vulvovaginitis. Efficacy was determined by evaluating the following: (i) the prevalence and intensity of symptoms (pruritus, burning and dysuria) and signs (erythema, leucorrhoea and oedema), and the evolution of symptoms and signs and intensities over time; (ii) the paediatrician's subjective opinion on the contribution of Zelesse® to the resolution of the symptoms and signs; (iii) the parent's subjective perception of improvement; (iv) the time to improvement; (v) the incidence of adverse events; (vi) the compliance with treatment. The prevalence and intensity of symptoms and signs were individually evaluated at baseline and after treatment. Intensities were graded as 0 = absence, 1 = mild intensity, 2 = moderate intensity and 3 = severe intensity. The evolution of symptoms and signs over time was determined by comparing their intensities at

baseline and at the end of the treatment and was categorized into four groups according to the outcome: cured (absence of the symptom/sign observed at baseline), improvement (decreased intensity of the symptom/sign observed at baseline), no change (same intensity at the end of the treatment as at baseline) and worsening (increased intensity of the symptom/sign observed at baseline). The GSS score,[16,17] a composite score of symptoms and signs (ranging between 0 and 18), was calculated by summing the individual intensities for each symptom and sign both at baseline and after treatment with Zelesse®. After treatment, paediatricians were asked about the contribution of Zelesse® to the resolution of the symptoms and signs ('great contribution', 'some contribution', 'slight contribution' or 'no contribution'); and parents or legal guardians were asked about their perception about the improvement of the symptoms and signs ('total recovery', 'great improvement', 'discreet improvement' or 'no changes'). When girls showed improvement, parents or legal guardians also reported the time to improvement: '2–3 days after starting the treatment', 'within the first week of treatment', 'after the first week of treatment' or 'at the end of the second week'. Tolerability was determined by the incidence of adverse events and the opinion of parents on this regard at the end of the treatment period. Parents or legal guardians evaluated the tolerability of the treatment by using an ad-hoc 5-point scale: 'very well tolerated', 'well tolerated', 'fairly well tolerated', 'poorly tolerated' or 'very poorly tolerated'. Acceptability was also evaluated by the opinion of the parents or legal guardians by using an ad-hoc 5-point scale: 'very well accepted', 'well accepted', 'fairly well accepted', 'poorly accepted' or 'very poorly accepted'). The treatment was considered very poorly accepted when girls refused to use the vaginal wash or cried during administration.

Statistical analyses

Considering previous studies of Zelesse® involving adult female patients with non-specific vulvovaginitis,[12,14,15] the estimated number of paediatric patients to be included in the study was 60. This sample size allowed for the estimation of the proportion of patients with good acceptance of the product for a 95% confidence interval (95% CI) and a precision of 13% (assuming that the expected proportion was 50%, the value for the largest sample size).

All statistical analyses were performed using the SAS® statistical package, version 9.3 (SAS Institute Inc., Cary, NC, USA). Unless indicated, results are shown for the intention-to-treat population. Descriptive analysis of qualitative variables such as the intensity of the symptoms and signs and GSS score was performed with absolute and relative frequencies (%), mean ± SD or the 95% CI according to a normal or not normal distribution of data. Descriptive analysis of quantitative variables such as the evolution of the intensity of the symptoms and signs and the GSS score at baseline and after treatment was performed using a Wilcoxon signed-rank test. A P-value < 0.05 was considered statistically significant.

Results

The study enrolled 71 female paediatric patients with symptoms and signs suggestive of non-specific vulvovaginitis. Seven patients dropped out of the study: not meeting the inclusion criteria due to having infectious vulvovaginitis, $n = 1$; lack of compliance with treatment, $n = 4$; and protocol deviation, $n = 2$. Although the patient with infectious vulvovaginitis was quickly excluded from the study, her data remained in the intention-to-treat analysis of the results. The patients had a mean ± SD age of 4.5 ± 1.9 years, were mainly Caucasian

(66 of 71 patients; 93.0%), 85.9% (61 of 71 patients) had no relevant clinical antecedents or concomitant diseases and 59.2% (42 of 71 patients) had a previous history of at least one previous episode of vulvovaginitis (Table 1). Some hygienic sanitary measures carried out by girls were as follows: frequently washing the intimate area with soap (41 of 71 patients; 57.7%); ensuring to dry the area after a bath (55 of 71 patients; 77.5%); or frequently using cotton clothing (68 of 71 patients; 95.8%). A total of 67 of 71 patients (94.4%) received Zelesse® during the whole treatment period, with the study cohort having a mean ± SD administration period of 15.2 ± 3.5 days. Zelesse® was administered once daily (21 of 71 patients; 29.6%), once or twice daily (as needed) (32 of 71 patients; 45.1%) or twice daily (18 of 71 patients; 25.4%).

At baseline, the most prevalent symptoms and signs were erythema (69 of 71 patients; 97.2%), burning (65 of 71 patients; 91.5%) and pruritus (63 of 71 patients; 88.7%); whereas after treatment, these were significantly reduced to 22.5% (16 of 71 patients), 8.5% (six of 71 patients), and 9.9% (seven of 71 patients), respectively, ($P < 0.001$) (Figure 1A). Additionally, a significant reduction in the mean intensity of the symptoms and signs was observed: pruritus decreased from 1.8 to 0.1 ($P < 0.001$), burning from 1.7 to 0.1 ($P < 0.001$) and

Table 1. Baseline demographic and clinical characteristics of paediatric patients ($n = 71$) with suspected non-specific vulvovaginitis enrolled in a prospective study to evaluate the efficacy, tolerability and acceptability of Zelesse®.

	Total $n = 71$
Age, years	4.5 ± 1.9
Race	
Caucasian	66 (93.0)
Latin American	3 (4.2)
Other	2 (2.8)
Weight, kg	19.3 ± 5.8
Height, cm	107.8 ± 14.2
Body mass index, kg/m^2	16.3 ± 1.7
Relevant clinical antecedents or concomitant diseases	
Yes	10 (14.1)
No	61 (85.9)
History of vulvovaginitis episodes	
Yes	42 (59.2)
No	29 (40.8)
Hygienic sanitary measures	
Washing the intimate area frequently with soap	41 (57.7)
Using sponges for washing the area	31 (43.7)
Ensuring to dry the area after a bath	55 (77.5)
Type of clothes frequently used	
Synthetic clothing	3 (4.2)
Cotton clothing	68 (95.8)
Use of tight-fitting clothing	6 (8.5)

Data presented as mean ± SD or *n* of patients (%).

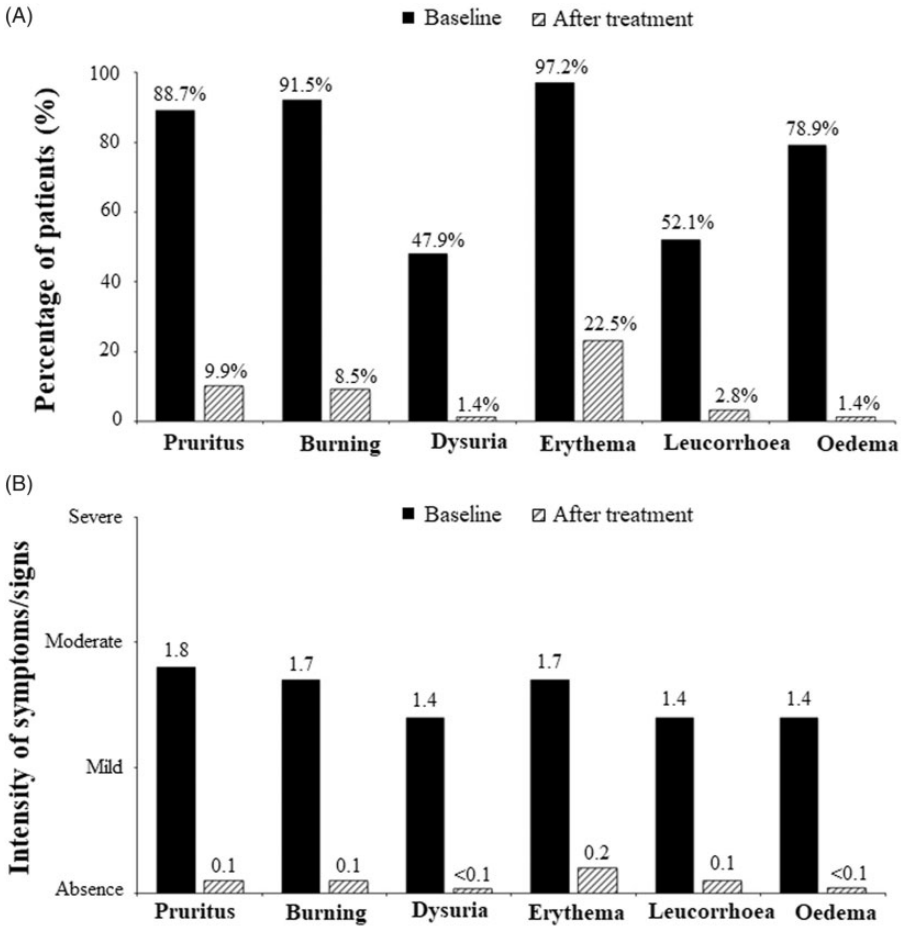

Figure 1. Prevalence (A) and evolution (B) of the intensity of symptoms and signs associated with non-specific vulvovaginitis in paediatric patients ($n = 71$) enrolled in a prospective study to evaluate the efficacy, tolerability and acceptability of Zelesse®. Data presented as percentage of patients in A and mean intensity score in B based on scores of 0 = absence, 1 = mild intensity, 2 = moderate intensity and 3 = severe intensity.

erythema from 1.7 to 0.2 ($P < 0.001$) (Figure 1B). All patients with moderate/severe pruritus or dysuria at baseline showed absence/mild intensity in these two symptoms after the treatment (Table 2). Moreover, 38 of 39 of patients (97.4%) with moderate/severe intensity of burning at baseline showed absence/mild intensity after the treatment. Similarly, 12 of 13 of patients (92.3%), 21 of 22 of patients (95.5%) and 44 of 45 of patients (97.8%) of patients with moderate/severe intensity of leucorrhoea, oedema and erythema, respectively, had significantly diminished intensity to absence/mild after treatment ($P < 0.001$). Pruritus disappeared in 56 of 63 patients (88.9%), burning in 59 of 65 patients (90.8%), dysuria in 33 of 34 patients (97.1%), erythema in 53 of 69 patients (76.8%), leucorrhoea in 35 of 37 patients (94.6%) and oedema in 55 of 56 patients (98.2%). A total of 47 of

Table 2. Evolution of the symptoms and signs associated with non-specific vulvovaginitis in paediatric patients.

	Pruritus $n=63$	Burning $n=65$	Dysuria $n=34$	Erythema $n=69$	Leucorrhoea $n=37$	Oedema $n=56$
Baseline						
Absence*	8 (11.3)	6 (8.5)	37 (52.1)	2 (2.8)	34 (47.9)	15 (21.1)
Mild	20 (31.7)	26 (40.0)	23 (67.6)	24 (34.8)	24 (64.9)	34 (60.7)
Moderate	37 (58.7)	31 (47.7)	8 (23.5)	38 (55.1)	12 (32.4)	22 (39.3)
Severe	6 (9.5)	8 (12.3)	3 (8.8)	7 (10.1)	1 (2.7)	0 (0.0)
After the treatment						
Absence*	64 (90.1)	65 (91.5)	70 (98.6)	55 (77.5)	69 (97.2)	70 (98.6)
Mild	7 (100.0)	5 (83.3)	1 (100.0)	15 (93.8)	1 (50.0)	0 (0.0)
Moderate	0 (0.0)	1 (16.7)	0 (0.0)	1 (6.3)	0 (0.0)	1 (100.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)
Evolution with treatment						
Cured	56 (88.9)	59 (90.8)	33 (97.1)	53 (76.8)	35 (94.6)	55 (98.2)
Improved	6 (9.5)	4 (6.2)	1 (2.9)	11 (15.9)	0 (0.0)	0 (0.0)
No changes	1 (1.6)	2 (3.1)	0 (0.0)	5 (7.2)	2 (5.4)	1 (1.8)

Data presented as *n* of patients (%).
*Calculated for 71 patients.

71 patients (66.2%) reported the absence of symptoms and signs of vulvovaginitis after treatment with Zelesse®. The mean GSS score for the entire cohort significantly decreased by 6.8 points; from 7.4 at baseline to 0.5 after the treatment ($P < 0.001$).

Paediatricians considered that treatment with Zelesse® had contributed greatly to the improvement of symptoms and signs in 61 of 71 patients (85.9%) (Figure 2A). Similarly, 65 of 71 parents/legal guardians (91.5%) perceived that Zelesse® greatly improved or totally resolved the symptoms and signs (Figure 2B). A total of 60 of 69 patients (86.9%) experienced the improvement during the first week of treatment (Figure 2C). Zelesse® was referred to be well/very well tolerated by 68 of 71 patients (95.7%) (Figure 3A). Only two of 71 patients (2.8%) reported poor or very poor tolerability. The acceptability was reported as being well/very well accepted in 66 of 71 patients (92.9%) (Figure 3B). Four of 71 patients (5.6%) reported an adverse event during the treatment, including itching (leading to definitive discontinuation; $n=1$), pruritus ($n=1$), pharyngitis (not related to the product, $n=1$); and intolerance (leading to definitive discontinuation; $n=1$). No serious adverse events were reported.

Discussion

The symptoms of non-specific vulvovaginitis can be adequately controlled with the adherence to hygienic sanitary measures and the treatment with topical products.[18] Zelesse® may be beneficial for the management of non-specific vulvovaginitis in young paediatric patients, as already demonstrated in adult females, by improving their most typical manifestations.[12,14,15] To date, there are no published studies that have evaluated the efficacy, tolerability and acceptability of Zelesse® in paediatric patients. Results from the present study demonstrated that Zelesse® produced a significant improvement in the prevalence and intensity of the symptoms and signs of non-specific vulvovaginitis in paediatric patients

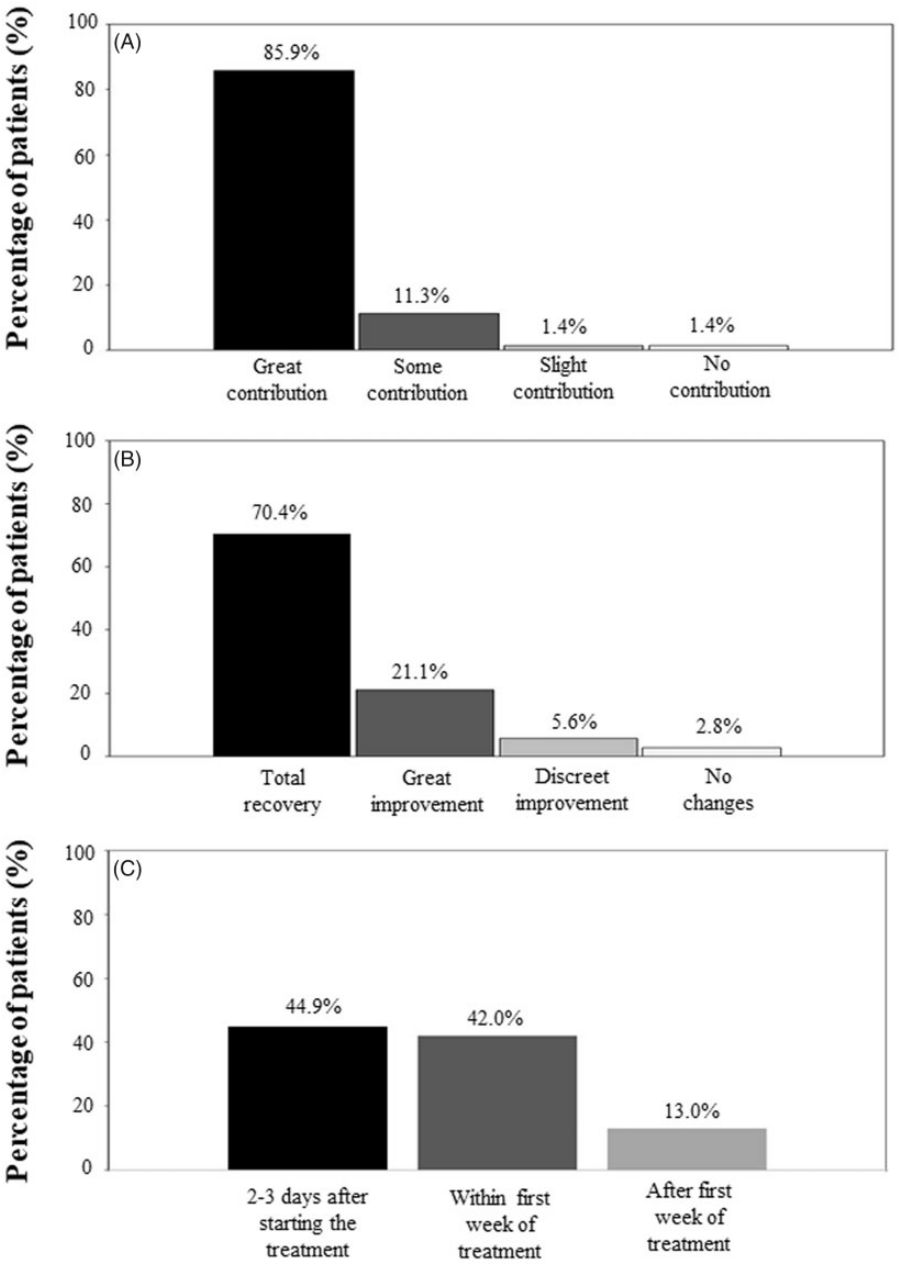

Figure 2. Paediatrician's (A) and parent's (B) opinion about the contribution made by the use of Zelesse® to the resolution and improvement of the symptoms and signs of non-specific vulvovaginitis in paediatric patients ($n = 71$). Parent's opinion about the time to improvement (C) in paediatric patients ($n = 69$).

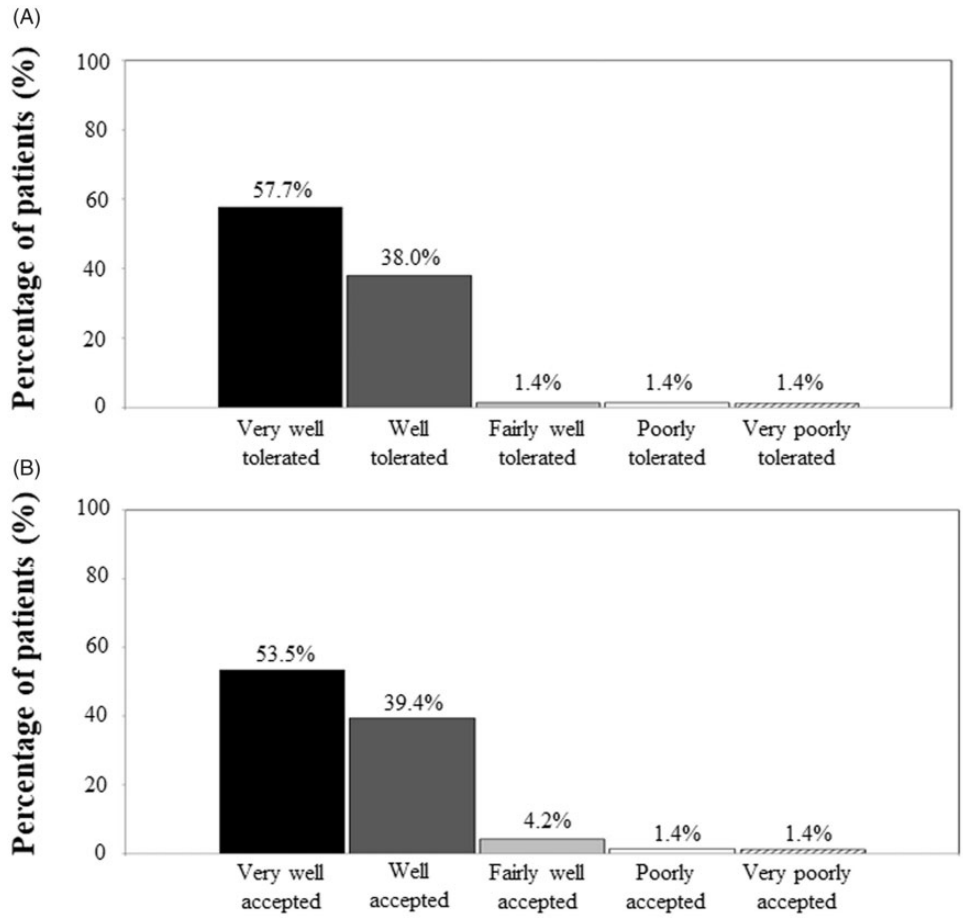

Figure 3. Tolerability (A) and acceptability (B) of Zelesse® indicated by parents after the treatment of paediatric patients with non-specific vulvovaginitis. Both figures show data from the intention-to-treat population ($n = 71$).

aged 2 to 8 years. Indeed, after receiving Zelesse® every symptom and sign diminished in the great majority of patients: approximately nine out of 10 patients presenting with any symptom or sign were cured (with the exception of erythema, which was cured in 76.8%) and two out of three symptomatic girls were cured (i.e. absence of all symptoms and signs).

Pruritus, burning and erythema are the most prevalent manifestations of non-specific vulvovaginitis reported in clinical practice and in the published literature.[1,3,7] Studies analysing the efficacy of topical products on symptoms and signs of non-specific vulvovaginitis are limited, especially in young girls. A prospective study involving 42 girls aged between 10 months and 12 years with symptoms and signs of vulvovaginitis such as pruritus (81%), leucorrhoea (50%) and erythema (71%), who received a soap-free cleansing solution for intimate hygiene once or twice daily for at least 1 week, demonstrated that symptoms and signs were improved after treatment.[19] In this current study, the majority of

significant manifestations of vulvovaginitis were improved or cured: pruritus in 98%, burning in 97%, dysuria in 100%, erythema in 93%, leucorrhoea in 95% and oedema in 98% of the patients that presented with the signs and symptoms at baseline. The improvement in pruritus and burning was considered clinically relevant as they are very distressing and persistent, and frequently they do not resolve without treatment.[20]

In this present study, Zelesse® was particularly effective against pruritus, which represents the most bothersome symptom and the most common reason why patients consult the doctor.[21] Pruritus causes discomfort and anxiety in girls, especially at night.[22] Nocturnal pruritus can impair the sleep and the quality of life of girls and their parents.[23] It is particularly important that pruritis is adequately managed in paediatric patients because secondary bacterial and fungal infections might appear as a result of scratching with poorly washed hands.[24,25] In the present study, pruritus improved and disappeared in 98% and 89% of the patients that presented with this symptom at baseline, respectively. In terms of intensity, 100% of the patients with moderate/severe pruritus at baseline presented with absence/mild pruritus after treatment. A very good response was also shown in leucorrhoea, a sign more frequent in older girls that appears as a consequence of the inflammatory response in the genital area.[26] In this present study, leucorrhoea was reported by 52% of girls at baseline and only remained in two of 37 patients (5.4%) after treatment. Erythema was the sign that showed the least pronounced improvement after treatment in the present study. At baseline, 97% of patients presented with erythema of various intensities and after treatment 23% still presented with this sign. Normally, erythema represents the most resistant sign and takes longer to disappear than the other typical manifestations.[27] In addition, this fact might be explained by the difficulty associated with evaluating the evolution of this sign in girls aged between 2 and 8 years. Erythema is frequently accompanied by local swelling, which can cause discomfort in contact with clothes or while performing activities such as walking or running. Normally, this swelling is not treated with concomitant medication. In terms of intensity, erythema decreased from 1.7 to 0.2, which represents a significant variation. These patients often develop non-specific erythema of mild intensity (most of the time it causes no pain) since this sign is associated with dentition and the use of diapers.

The present study demonstrated that Zelesse® showed a great improvement in the evolution of all of the evaluated symptoms and signs of non-specific vulvovaginitis in paediatric patients. In fact, more than 92% of girls with moderate or severe symptoms or signs diminished the intensity to mild or absence after the treatment and the GSS score showed that intensity was reduced from 7.4 to 0.5 after the treatment.

In this current study, 59.2% of patients had history of at least one previous episode of vulvovaginitis. This prevalence of recurrence was in concordance with investigator's clinical practice and the published literature.[28,29] Girls mainly attend the doctor due to the irritation of the genital area and this is rarely due to a lack of hygiene. Hygienic sanitary measures appear to be associated with the socioeconomic level of the patients.[30] Patients from this present study were derived mainly from private paediatrician offices, which suggests a medium-to-high socioeconomic level. This fact was in accordance with the hygienic sanitary measures reported at baseline, i.e. washing the intimate area frequently with soap (57.7%), ensuring to dry the area after a bath (77.5%), wearing cotton clothing (95.8%) and avoiding tight-fitting clothing (91.5%).

The present study demonstrated that the effects of Zelesse® on the symptoms and signs of non-specific vulvovaginitis were rapidly observed; in 44.9% of cases the improvement was shown after 2–3 days and most responses were observed within the first week of treatment. Both paediatricians and parents agreed in terms of their opinion that Zelesse® greatly contributed to the resolution/total recovery of the symptoms and signs of non-specific vulvovaginitis. Furthermore, it was well accepted and tolerated by most of the paediatric patients. Indeed, only four patients (5.6%) reported an adverse event during treatment and none of them were considered serious.

This present study had several limitations. First, the study did not include a control or placebo group for comparison purposes, especially for the evaluation of efficacy. However, it was not considered fully necessary for this preliminary study, which is the first investigation performed in paediatric patients.[12,14,15,19] Secondly, the study design was limited because there were only two visits for clinical evaluation (baseline and after the treatment). More time points would increase the knowledge about the evolution of the symptoms and signs of vulvovaginitis during the treatment period. In our opinion, the design of the present study was useful as it allowed for the preliminary investigation of the efficacy of Zelesse® for the management of non-specific vulvovaginitis in paediatric females. Further studies, involving larger cohorts of patients, with more follow-up time points and with control groups, would be required to corroborate these initial findings.

In conclusion, Zelesse® is an intimate hygiene wash solution, which was very effective for the relief of the symptoms and signs of non-specific vulvovaginitis in females aged between 2 and 8 years. Zelesse® was particularly effective against pruritus, burning and erythema, which are the most prevalent and intense problems observed in young females with non-specific vulvovaginitis. These three symptoms and signs are usually persistent and hard to resolve without adequate management. Improvements were observed quickly and Zelesse® was well accepted, well tolerated and very few adverse events were reported.

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References

1. Joishy M, Ashtekar CS, Jain A, et al. Do we need to treat vulvovaginitis in prepubertal girls. *BMJ* 2005; 330: 186–188.
2. Pierce AM and Hart CA. Vulvovaginitis: causes and management. *Arch Dis Child* 1992; 67: 509–512.

3. Stricker T, Navratil F and Sennhauser FH. Vulvovaginitis in prepubertal girls. *Arch Dis Child* 2003; 88: 324–326.
4. Cuadros J, Mazón A, Martinez R, et al. The aetiology of paediatric inflammatory vulvovaginitis. *Eur J Pediatr* 2004; 163: 105–107.
5. Emans SJ and Goldstein DP. The gynecologic examination of the prepubertal child with vulvovaginitis: use of the knee-chest position. *Pediatrics* 1980; 65: 758–760.
6. Vandeven AM and Emans SJ. Vulvovaginitis in the child and adolescent. *Pediatr Rev* 1993; 14: 141–147.
7. Garden AS. Vulvovaginitis and other common childhood gynaecological conditions. *Arch Dis Child Educ Pract Ed* 2011; 96: 73–78.
8. Cemek F, Odabaş D, Şenel Ü, et al. Personal hygiene and vulvovaginitis in prepubertal children. *J Pediatr Adolesc Gynecol* 2016; 29: 223–227.
9. Fivozinsky KB and Laufer MR. Vulvar disorders in prepubertal girls. A literature review. *J Reprod Med* 1998; 43: 763–773.
10. Laufer MR and Emans SJ. Overview of vulvovaginal complaints in the prepubertal child. UpToDate®. Available at: http://www.uptodate.com/contents/overview-of-vulvovaginal-complaints-in-the-prepubertal-child [accessed 08 July 2017].
11. Zelesse. Brochure of product. Italfarmaco. Available at: www.zelesse.com/documents/708881/14232616/prospecto_zelesse_230514_web.pdf [accessed 08 July 2017].
12. Delgado Marín JL, Oliva Sánchez R, San Martín Moral R, et al. Eficacia de una nueva solución para el lavado y la higiene íntima sobre los síntomas y signos de la vulvovaginitis aguda. Poster presented at: XIX SEMERGEN Congress; 6–7 June; 2014; Valencia (Spain).
13. Argüelles Martínez E, Delgado Marín JL, Blanco Carnero JE, et al. Utilidad de Zelesse® una nueva solución de higiene intima como coadyuvante en el tratamiento de las vulvovaginitis agudas de causa infecciosa. Abstract XIX SEMERGEN Congress; 6–7; 2014; Valencia (Spain).
14. San Martin R, Delgado JL, Oliva R, et al. Zelesse a new intimate hygiene wash solution for the relief of symptoms and signs of acute vulvovaginitis. Poster presented at: The 20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI); 4–7 December; 2014; Paris (France).
15. Delgado JL, Oliva R, Blanco JE, et al. Zelesse®, a new intimate hygiene wash solution for the relief of symptoms and signs of acute nonspecific vulvovaginitis. Poster presented at: The International Congress of the French Society of Gynecology; 2014.
16. US Dept. Health and Human Services (2003). Guidance for Industry: Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms - Recommendations for Clinical Evaluation. Draft Guidance. Washington: U.S. Department of Health and Human Services. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071643.pdf. [accessed 06 April 2018].
17. Cano A, Estévez J, Usandizaga R, et al. The therapeutic effect of a new ultra low concentration estriol gel formulation (0.005% estriol vaginal gel) on symptoms and signs of postmenopausal vaginal atrophy: results from a pivotal phase III study. *Menopause* 2012; 19: 1130–1139.
18. Aruda MM. Vulvovaginitis in the prepubertal child. *Nurse Pract Forum* 1992; 3: 149–151.
19. Berlier P. [Cuidados en la higiene vulvo perineal a propósito del seguimiento de 42 casos del uso de saforelle en niñas]. Article in Spanish. Study presented at: III Rencontres Alfred Fournier Meeting; June; 1990; Cannes (France). Available at: http://pediagess.com/archivos1pdf/Saforelle%20solucion%20-%20higiene%20vulvo%20perineal.pdf. [accessed 08 July 2017].
20. Lambert J. Pruritus in female patients. *Biomed Res Int* 2014; 2014: 541867.
21. Masero Casasola AR, Guillán Maquieira C, San Frutos Llorente L, et al. Alivio del prurito en mujeres con vulvovaginitis aguda mediante el uso de una crema íntima a base de Camomila, Bardana y Aloe Vera. Estudio Zelina. Poster – SEGO Congress, 2017, Oviedo; Spain.
22. Fischer G. Vulval disease in childhood. *Aust Prescr* 2005; 28: 88–90.

23. Lavery MJ, Stull C, Kinney MO, et al. Nocturnal pruritus: The battle for a peaceful night's sleep. *Int J Mol Sci* 2016; 17: 425.
24. Healthychildren.org. Vaginal symptoms. Available at: https://www.healthychildren.org/English/tips-tools/symptom-checker/Pages/symptomviewer.aspx?symptom=Vaginal+Symptoms [accessed 08 July 2017].
25. Jain A, Jain S and Rawat S. Emerging fungal infections among children: A review on its clinical manifestations, diagnosis, and prevention. *J Pharm Bioallied Sci* 2010; 2: 314–320.
26. Hayes L and Creighton SM. Prepubertal vaginal discharge. *The Obstetrician & Gynaecologist* 2007; 9: 159–63.
27. Fischer G. Coping with chronic vulvovaginal candidiasis. *Medicine Today* 2014; 15: 33–40.
28. Powell AM and Nyirjesy P. Recurrent vulvovaginitis. *Best Pract Res Clin Obstet Gynaecol* 2014; 28: 967–976.
29. Sobel JD. Recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2016; 214: 15–21.
30. Arbour M, Corwin EJ and Salsberry P. Douching patterns in women related to socioeconomic and racial/ethnic characteristics. *J Obstet Gynecol Neonatal Nurs* 2009; 38: 577–585.