

# Perceived Efficacy of Vaginal Dryness Relief: A Comparative Clinical Study between *Sodium hyaluronate vaginal gel*<sup>1</sup> vs. *Promestriene cream*<sup>2</sup>

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**How to cite this paper:** Duque-Estrada, E. de O., Rosa, V.P., Mosca, M.M. and do Nascimento, H.L. (2017) Perceived Efficacy of Vaginal Dryness Relief: A Comparative Clinical Study between *Sodium hyaluronate vaginal gel* vs. *Promestriene cream*. *Advances in Sexual Medicine*, 7, 34-43.

<http://dx.doi.org/10.4236/asm.2017.71003>

**Received:** November 18, 2016

**Accepted:** January 15, 2017

**Published:** January 18, 2017

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## Abstract

In the study, we report the comparative efficacy of the sodium hyaluronate gel vaginal application and *promestriene cream* which were tested to treat the gynecological symptoms of people who suffered from vaginal dryness. *Method:* 35 patients applied *sodium hyaluronate vaginal gel* one time a day for a period of two times a week during three weeks and other 33 patients using *promestriene cream* applied it every day for a period of three weeks also. *Results:* No significant difference was observed between vaginal application of sodium hyaluronate gel and *promestriene cream*, regarding both, as regarding the dryness of the intimate mucosa ( $p = 0.786$ ), the attribute of moisturizing properties to the intimate mucosa ( $p = 0.142$ ), the comfort sensation ( $p = 0.528$ ), and no significant difference was observed regarding the fragrance of the product ( $p = 0.088$ ). *Conclusion:* The similar results between vaginal application of both products support the use of sodium hyaluronate vaginal gel (Lubrinat®) in the initial approach of symptoms of vaginal dryness.

## Keywords

Vaginal Dryness, Menopause, Sodium Hyaluronate, Promestriene

## 1. Introduction

Menopause is the permanent cessation of menses, after 12 consecutive months of amenorrhea. This can occur naturally or be induced secondary to the follicular depletion by bilateral oophorectomy, radiation to the ovaries, or by chemotherapy effects on ovarian follicular reserves [1] and the vaginal atrophy is common in postmenopausal women

<sup>1</sup>Sodium hyaluronate vaginal gel: Lubrinat®.

<sup>2</sup>Promestriene vaginal cream: Colpotrofine®.

and negatively affects the quality of life [2].

On the vaginal dryness symptom, it is estimated that 10% to 50% of postmenopausal women have symptoms related, which include vulvovaginal irritation and dyspareunia [3] [4]. These symptoms will progress markedly and unfortunately will not be solved without treatment [5]. The epidemiologic data on post-menopause women evolution confirm that only 25.0% of them refer for treatment [6] [7] [8]. So, these events have a significant impact on women's quality of life [9] [10].

The therapeutic solution for vaginal dryness is systemic and/or topically applied products that hydrate the vaginal mucosa. The vaginal topic treatment with estrogen is effective in reversing atrophic vaginal changes and relieving symptoms [11] [12]. However, the patients are aware of the possible relationship between cancer, heart disease, stroke, and estrogen-based treatments, which means that many patients are reluctant to use such formulations [13]. Hyaluronic acid vaginal gel (Lubrinat®, Master farmacêutica, Brazil) is a colorless gel that has been marketed in Brazil since 2015. The gel's hydrating properties are attributed to the characteristics of this hyaluronic acid-based biopolymer that releases water molecules to the tissue, thus alleviating the dry state of the vagina. Following these statements, we propose to do a comparative study on a non-hormonal gel-hyaluronic acid formulation—in front a hormonal cream promestriene—to treat the symptomatic vulvovaginal atrophy (VVA).

### **Aim**

The present study aimed to evaluate the subjective perception of the efficacy in relieving vaginal dryness. We tested the hypothesis that the efficacy of (non-hormonal) sodium hyaluronate gel for the vaginal application (Lubrinat®) is not inferior to that of (hormonal) promestriene (Colpotrofine®) vaginal cream for the treatment of vaginal dryness symptoms.

## **2. Material and Methods**

The recruitment of the gynecologic participants was conducted by the Clinical Research Office (CRO) Allergisa Pesquisa Dermato-Cosmética Ltda. located in Campinas, São Paulo, Brazil. The participants were informed of the purpose of the study, its methodology and duration, the advantages and medical restrictions related to the study. The participants confirmed their interest in participating by signing the informed consent.

The study was approved by and carried out in accordance with the ethical standards of the Ethics Committee.

The study was conducted in accordance with the Declaration of Helsinki and in compliance with the CNS Resolution No. 466/12 of ANVISA, and also in accordance with Good Clinical Practice (Document of the Americas and ICH E6: Good Clinical Practice). The technical documentation and files from this study will be kept for a period of 5 years.

### ***Subjects and Study Design***

The open-label, prospective, randomized and controlled study occurred between 10/19/2015 and 11/10/2015 under the code All-E-EP-052818-01/10.02.15. The total duration of the study was 21 days (+/-2 days) of product use.

The *Inclusion Criteria* was:

- The capacity to consent to participate in the study;
- Female and postmenopausal;
- Age between 40 - 70;
- Dryness complaint in the vaginal region;
- Skin and mucosa intact in the test region;
- Concordance to adhere to the procedures and requirements of the test;
- Concordance to attend the institute at day(s) and time(s) set for evaluations;

The *exclusion criteria* was

- Past record of reaction to the category of the tested products;
- A skin condition in the product application area;
- Skin diseases like:
  - Psoriasis;
  - Vitiligo;
  - Atopic dermatitis;
  - Immunologic failure;
  - Diabetes Mellitus Type 1;
  - Insulin-dependent diabetes;
  - Presence of complications due to diabetes (e.g., retinopathy, nephropathy, neuropathy);
  - The presence of dermatosis related to diabetes (e.g. plantar ulcer, lipoid necrobiosis, granuloma annulare, opportunistic infections);
  - History of hypoglycemia, diabetic ketoacidosis and/or hyperosmolar and coma;
  - Current use of the following medications for topical or systemic use of Corticosteroids, Immunosuppressant drugs and Antihistamine;
  - Other disorders or medication that may interfere directly in the study or even endanger the health of the research participant.

The primary aim of this study was to assess the efficacy and safety of hyaluronic acid vaginal gel in front of promestriene cream in the treatment of symptoms of vaginal dryness. The total of patients observed (the study sample size) was designed to obtain at least 60 responses in each evaluation arm, distributed by a randomization method, according to the Cosmetic Safety Assessment Guide of Brazilian Health Surveillance Agency (ANVISA). The Group “A” (Lubrinat®) applied one applicator of the drug 1 time a day for a period of two times a week during three weeks and group “B” (Colpotrofina®) used one applicator every day for a period of three weeks also. The manner of putting the cream inside the vagina and using it at a specified time was explained for both groups and followed-up by telephone calls. The comparison between the treatments was performed using the nonparametric *Mann-Whitney test*. The evaluation of the efficacy was carried out through the application of Perceived Efficacy questionnaires based on the “Standard Guide for Sensory Claim substantiation” of the American Society for Testing and Materials (ASTM) [14].

For its application, the participants were asked to evaluate their sensation at the following times:

- **T0:** At the first day of the study, before application of the test product, the profile

summary of the Research Participant was completed and the attributes at issue evaluated by the participants (1) “Dryness” and (2) “Comfort Sensation”.

- **T21:** After 21 +/- 2 days of use of the product (Perceived Efficacy), the statement evaluated by the participants was “The product has moisturizing properties to the intimate mucosa”. In this evaluation, the attributes (1) “Dryness” and (2) “Comfort Sensation” (3) “Product Fragrance” (4) “Ease of Application” and (5) “The product has moisturizing properties to the intimate mucosa” were still evaluated.

### 3. Results

74 female participants were recruited for the study, with ages between 42 and 67 years, but 4 of those selected did not meet the study criteria. From these 70 participants who began the study, 01 had an adverse event and 01 patient gave up participation for personal reasons unrelated to the study. Overall, 68 participants completed the study (Table 1).

Completed the study 68 participants, but one (01) of these had an adverse event. Regarding the study disconnections, one (01) dropped the assessment study because of unrelated personal reasons and another was excluded from the study for presenting an adverse event-abdominal discomfort in the hypogastric region-considered no causal relationship to the product under test.

#### Initial Symptoms of Research Participants (T0)

The number of research participants was equal to 35 for the treatment (01) and 33 for the treatment (02). The confidence level considered in the comparative analysis was 95%. Note that the percentages of perceived efficacy results are inserted in the tables with a decimal place after the comma. Due to this rounding, some percentages when added manually by the rounded table data may be equal to 100.1% or 99.9%. Table 2 and Table 3 show the results of the evaluation of the participants at the time T0 for the test products.

**Table 1.** Age characteristics in the study groups.

Variables	Group “A” (Lubrinat®) (n = 35)	Group “B” (Colpotrofine®) (n = 33)	P value
Age (year) Mean ± SD	56.7 ± 5.7	55.2 ± 5.5	0.28

\*Frequency Mean ± SD Chi-square.

**Table 2.** Evaluation of perceived efficacy of Group “A” (Lubrinat®) (T0\*).

Regarding dryness, your intimate mucosa is	Very dry	54.3%
	Dry moderately	42.9%
	A Little dry	2.9%
	Not dry	0%
Regarding comfort sensation, your intimate mucosa is	Very comfortable	2.9%
	Comfortable moderately	42.9%
	Little comfortable	8.6%
	Don't feel comfortable	45.7%

\*T0 = first day of the study.

**Table 3.** Evaluation of perceived efficacy of Group “B” (Colpotrofine<sup>®</sup>) (T0\*).

Regarding dryness, your intimate mucosa is	Very dry	57.6%
	Dry moderately	42.4%
	A Little dry	0%
	Not dry	0%
Regarding comfort sensation, your intimate mucosa is	Very comfortable	3%
	Comfortable moderately	36.4%
	Little comfortable	21.2%
	Don't feel comfortable	39.4%

\*T0 = first day of the study.

### Final Evaluation of Perceived Efficacy by the Research Participants (T21)

The **Table 4** and **Table 5** below show the percentage of participants who reported acceptance for attributes and perceived efficacy results evaluated after 21 +/- 2 days of use of products on the test (T21).

For the attribute Dryness, it was considered as the sum of categories “slightly decreased”, “moderately decreased” and “decreased a lot”.

For the attribute Comfort Sensation, it was considered as the sum of categories “slightly increased.”, “moderately increased” and “increased a lot”.

For the attribute Fragrance of the product, it was considered as the sum of categories “liked it slightly”, “liked moderately”, “I liked a lot” and “loved”.

For the attribute Ease of Application, it was considered as the sum of categories “a little easy”, “easy” and “very easy”.

## 4. Discussion

During the menopause, many physiological occurrences influence both symptomatology and sexuality, including the vulvovaginal dryness symptoms [15] [16] affecting well-being [17]. The female urogenital aging in consequence of declining levels of estrogen-producing atrophic changes [18].

The vulvovaginal dryness at menopausal women is clearly associated with the reduction of estrogen circulation, resulting in the reduction of skin elasticity and collagen, and the consequent vaginal atrophy [3] [19] [20] [21]. If vasomotor symptoms tend to disappear with time, vulvovaginal atrophy tends to worsen continuously [22] [23] [24], and according to the North American Menopause Society (NAMS) “*the initial clinical approach of vaginal atrophy should relieve the symptoms with non-hormonal lubricants and moisturizers therapies, as well as the maintenance of sexual activity. At the time that vaginal moisturizer does not offer relief, topical estrogen therapy should be applied considering the isolated complaint of vaginal dryness*” [25].

We must consider that for symptoms relating to dryness, pruritus, and dyspareunia, non-hormonal vaginal lubricants/moisturizers are commonly used, and presumably the major reasons for this relate to their ready availability over-the-counter and the ability of the individual to avoid a physician’s consultation [26]. In this context and observing the orientation of the Brazilian Federation of Gynecology and Obstetrics Associations

**Table 4.** Perceived efficacy results.

REPRESENTATIONS	Lubrinat (T21#)	Promestriene (T21#)	P Value (2)
The product has moisturizing properties for the intimate mucosa.	94.3 (%)	97 (%)	0.142

1) For the above statement, it was considered the sum of categories “*Totally agree*” and “*Agree*”; 2) \*\*\*significant at the 0.1% level; \*\*significant at the 1% level; \*significant at 5% (Mann-Whitney test); #T21 = Last day of the study.

**Table 5.** Perceived efficacy results.

KEY ATTRIBUTES	Lubrinat (T21#)	Promestriene (T21#)	P Value (1)
Dryness	97 ± 1	100	0.786
Comfort Sensation**	88.6 (%)	90.9 (%)	0.528
Fragrance Product***	88.6 (%)	78.8 (%)	0.088
Ease of Product Application****	100	84.8 (%)	0.123

#T21 = Last day of the study. 1) \*\*\*significant at the 0.1% level; \*\*significant at the 1% level; \*significant at 5% (Mann-Whitney test).

(FEBRASGO), the “Medical assistance to postmenopausal women should be directed to the maintenance of their health, and quality of life, and preventive aspects” [27], it justifies the search for new therapeutic approaches in this moment of life, and our present study.

Both menopausal and postmenopausal women have many symptoms related to low levels of estrogen, with most cases of symptomatic vaginal claims requiring treatment; however, only about 25% of symptomatic women seek medical help [20]. It has been recognized that providing women with the opportunity to talk about sexual problems is a fundamental aspect of healthcare [28] and a brief enquiry into such matters by healthcare professionals can prove itself to be valuable [29], but an International Survey performed in young women (18 - 44 years) from 13 countries confirmed that less than 50% of the women was comfortable talking to healthcare professionals about vagina-related issues [30]. The main factors are a culturally dependent lifestyle that contributes to sexual attitudes across the menopause [31].

For hormonal methods, the both systemic and/or topical conjugated estrogen in are prescribed [11] [32] [33] [34]. We decided for a comparative test to Promestriene cream, which is a synthetic estrogen analog, a diethyl-ether of estradiol available as a vaginal cream or ovule. The Promestriene acts on vaginal atrophy without acting on the endometrium or stimulating gonadotrophins/estrogen plasma levels [35] [36] [37] [38]. In several small open-label studies, it was proved to significantly improve vulvovaginal trophicity in both naturally and surgically menopausal women with minimal absorption. According to Santos and Clissold [35] it has two important attributes:

1) Firstly, it is very poorly absorbed by the vagina and does not affect systemic hormone levels or estrogen activity. The minimal (51%) absorption of Promestriene mostly occurs at the very beginning of the treatment, as a consequence of the atrophic vaginal

mucosa being thin and having several micro-fissures. With the treatment, the epithelium becomes eutrophic and no further absorption occurs;

2) It has demonstrated anti-atrophic activity in the genitourinary tract and this has resulted in significantly improved symptoms associated with vaginal atrophy.

Regarding the hyaluronic acid, which is a natural polysaccharide, it can be mentioned that it forms an important part of the extracellular matrix of the skin and cartilage [39] [40] [41]. Hyaluronic acid is a glycosaminoglycan and relative to its molecular weight, it may bind huge amounts of water making it a promising ingredient for a moisturizer. Indeed, hyaluronic acid vaginal gel has been studied in postmenopausal women previously [33] [42].

The hyaluronic acid vaginal gel has no hormone-like effect; thus, it had no influence on the endometrium or the hormone-endocrine system and had a high safety profile. Compared with Promestriene cream, the hyaluronic acid vaginal gel has the characteristics of wider applicability, no hormone-like effect, higher safety, and better acceptability by patients [43]. The use of hyaluronic acid provided relief of the vaginal symptoms, improved epithelial atrophy, decreased vaginal pH and increased maturation of the vaginal epithelium [40].

To treat the Symptomatic Vulvovaginal Atrophy (VVA) the North American Menopause Society (NAMS) 2013 position statement says the primary goal of treating symptomatic VVA is 1) to alleviate symptoms and 2) for the woman with symptomatic VVA unrelated to sexual activity and for whom all other causes of her symptoms have been eliminated, first-line therapies include non-hormonal, long-acting vaginal moisturizers and low-dose vaginal estrogen, assuming no contraindications. When symptomatic vaginal atrophy does not respond to these options, hormonal prescription medication may be necessary [44]. The primary aim of this study was to assess the efficacy and safety of hyaluronic acid vaginal gel in front of Promestriene cream in treating the symptoms of vaginal dryness. The Evaluation of Efficacy was carried out through the application of Perceived Efficacy questionnaires based on the “Standard Guide for Sensory Claim substantiation” of the American Society for Testing and Materials (ASTM) [14]. This guide covers reasonable practices for designing and implementing sensory tests that validate claims pertaining only to the sensory or perceptual attributes, or both, of a product. The limitation of the present study was the short duration of the observation, but the symptoms improvement results on the no significant difference regarding all patients in both non-hormonal treatment (group “A”) and the hormonal treatment (group “B”) by T21 day (**Table 6**).

**Table 6.** Summary of conclusions on the evaluation of Perceived Efficacy Lubrinat® vs Promestriene.

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- No significant difference was observed between the products regarding the attribute “The product has moisturizing properties to the intimate mucosa” ( $p = 0.142$ ).
  - No significant difference was observed regarding the dryness of the intimate mucosa ( $p = 0.786$ ).
  - No significant difference was observed regarding comfort sensation in the intimate mucosa ( $p = 0.528$ ).
  - No significant difference was observed regarding the fragrance of the product ( $p = 0.088$ ).
  - No significant difference was observed regarding ease of application ( $p = 0.123$ ).
-

## 5. Conclusion

This evaluation study of the Perceived Efficacy as therapeutic innovation-Lubrinat® (sodium hyaluronate) supports its use in the initial approach of symptoms of vaginal dryness, according to the North American Menopause Society (NAMS) 2013 position statement which says the primary goal of treating symptomatic vulvovaginal Atrophy (VVA) (**Table 6**). Vaginal dryness can be helped by Lubrinat® (sodium hyaluronate). It's the most logical treatment to use in vaginal dryness since it's a modern, biotech, safe and well-tolerated product.

## Conflict of Interest

The authors have no conflicts to report during the study.

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