Perceived Efficacy of the relief of vaginal dryness: a comparative clinical study between Sodium hyaluronate vaginal * *vs.* Promestriene ** in actual use conditions.

Key words: sodium hyaluronate, promestriene, vaginal dryness

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* Sodium hyaluronate vaginal gel: Lubrinat®

** Promestriene vaginal cream: Colpotrofine®

Authors

Eduardo de Oliveira Duque Estrada[£]

Vivian Pessoto Rosa[¥]
Mariane Martins Mosca[¥]
Heliara Lopes do Nascimento[¥]

[£] Physician of Master Pharmaceutical
[¥]: Allergisa Team

Abstract

The symptoms of vaginal atrophy are frequent in postmenopausal women according to the North American Menopause Society (NAMS) the first-line therapies for women with vaginal atrophy are non-hormonal lubricants and moisturizers, as well as maintenance of sexual activity. In the present study the reports of efficacy are presented in subjective perception of the efficacy of vaginal dryness relief with the use of a vaginal application of sodium hyaluronate gel (Lubrinat®) and a vaginal application of promestriene cream (Colpotrofine®) in real conditions of use by women.

INTRODUCTION

The symptoms of vaginal atrophy are frequent in postmenopausal women. It is estimated that 10% to 50% of postmenopausal women have symptoms related to vaginal atrophy, vaginal dryness and include vulvovaginal irritation and dyspareunia. (1,2)

It is emphasized that these events have a significant impact on women's quality of life, so the majority of patients with symptomatic vaginal atrophy require treatment, but only about 25% of symptomatic women seek medical help. (3,4)

According to the North American Menopause Society - NAMS) the main objectives of the clinical approach of vaginal atrophy are relieving symptoms and reverse atrophic anatomic

changes. NAMS cites as first-line therapies for women with vaginal atrophy are non-hormonal lubricants and moisturizers, as well as maintenance of sexual activity. When symptomatic vaginal atrophy not respond to these options, hormonal prescription medication may be necessary. (5)

OBJECTIVES

The effects of the present study were to evaluate the subjective perception of the efficacy in relieving vaginal dryness using a sodium hyaluronate gel for vaginal application (Lubrinat®) and promestriene cream (Colpotrofine®) in conditions of actual use.

MATERIAL AND METHODS

The open-label, prospective, randomized and controlled study occurred between 10/19/2015 and 11/10/2015 under the code **AII-E-EP-052818-01 / 10.02.15.** The total duration of the study was 21 days (+/- 2 days) of product use. The recruitment of participants was conducted by the Research Center of Allergisa Pesquisa Dermato-Cosmética Ltda. located in Campinas, São Paulo, Brazil.

The study was conducted in accordance with the Declaration of Helsinki and according to CNS Resolution No. 466/12 of ANVISA, and in accordance with Good Clinical Practice (Document of the Americas and ICH E6: Good Clinical Practice).

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 technical documentation and files from this study will be kept for a period of 5 years.

The inclusion and exclusion criteria for the study are presented in Tables I, II and III.

The evaluation of Efficacy was carried out through the application Perceived Efficacy questionnaires based on the "Standard Guide for Sensory Claim substantiation" of the American Society for Testing and Materials (ASTM) (ASTM E 1958-06, 2006) The study aimed to obtain at its final at least 60 responses, according to the Cosmetic Safety Assessment Guide of Brazilian Health Surveillance Agency)- ANVISA.

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 product test, the profile summary of the Research Participant was completed and the attributes at issue evaluated by the participants (1) "*Dryness"* and (2)*"Comfort Sensation".*

- ***T*21:** 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) "D*ryness "* and (2)*"Comfort Sensation" (3) "Fragrance*

Product" (4) "Ease of Application " and (5) "The product has moisturizing properties to the intimate mucosa" were still evaluated.

The comparison between the treatments was performed using the nonparametric Mann-Whitney test. 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 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 I. Inclusion criteria in the study

- Capacity to consent participation in the study;
- Female and postmenopausal;
- Ages of 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 (s) day (s) and time (s) set (s) for evaluations;

Table II Non-inclusion criteria for the study

- Background reaction to the category of the tested product;
- skin condition in the product application area;
- Skin diseases: psoriasis, vitiligo, atopic dermatitis;
- immunologic failure;
- Diabetes Mellitus Type 1
- Insulin dependent diabetes;
- Presence of complications due to diabetes (eg, retinopathy, nephropathy, neuropathy.);
- presence of dermatosis related to diabetes (. ex plantar ulcer, lipoid necrobiosis lipoidica, granuloma annulare, opportunistic infections);
- History of hypoglycemia, diabetic ketoacidosis and / or hyperosmolar coma;
- Current use of the following medications for topical or systemic use:
    - 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.

Table III Study exclusion criteria

- Participants presenting, at the vision of the investigator, any problem that prevent continuity of product applications at any period of the study;
- Withdrawal of consent by the research participant, regardless of the reason;
- Lack of adherence of the research participant to the study. Shall be considered significant lack of adhesion when the participant does not attend the center for evaluations;
- Adverse Event Severe,
- Disorder or concurrent treatment any disease process or treatment that occurs during the course of the study and may interfere with the study product as drug interaction or could mask the results.

RESULTS

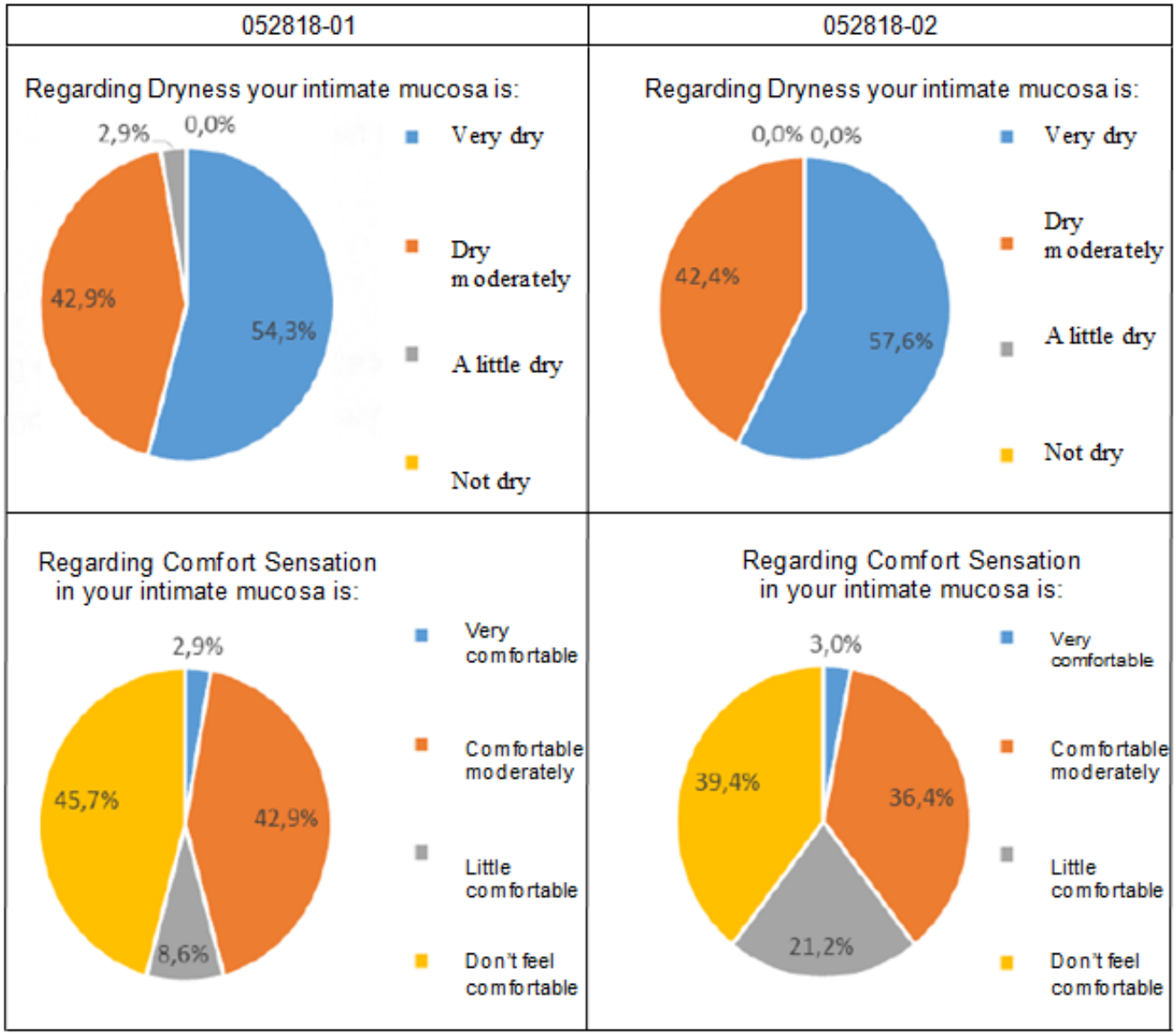
Were recruited for the study 74 female participants with ages between 42 and 67 years, but 4 selected did not meet the study criteria. From these 70 participants who began the study, 01 had an adverse event and 01 patient gave up participation for personal reasons unrelated to the study. Completed the study 68 participants

Completed the study 68 participants one (01) of these had an adverse event. Regarding to the study disconnections one (01) dropped by unrelated personal reason assessment study and other was withdrawal from the study for presenting adverse event - abdominal discomfort" in the hypogastric region - considered no causal relationship to the product under test.

Profile of Research Participants (T0)

Charts I to IV presented the results of the evaluation of the participants at the time T0 for the product test.

Figure I: Evaluation of Perceived Efficacy Lubrinat ® vs Promestriene at baseline. **T0**



Lubrinat **Promestriene**

Evaluation of Perceived Efficacy by the Research Participants (T21)

The tables below show the percentage of participants who reported acceptance for attributes and affirmation evaluated after 21 +/- 2 days of use of the product (T21).

Table I. Perceived Efficacy Results

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

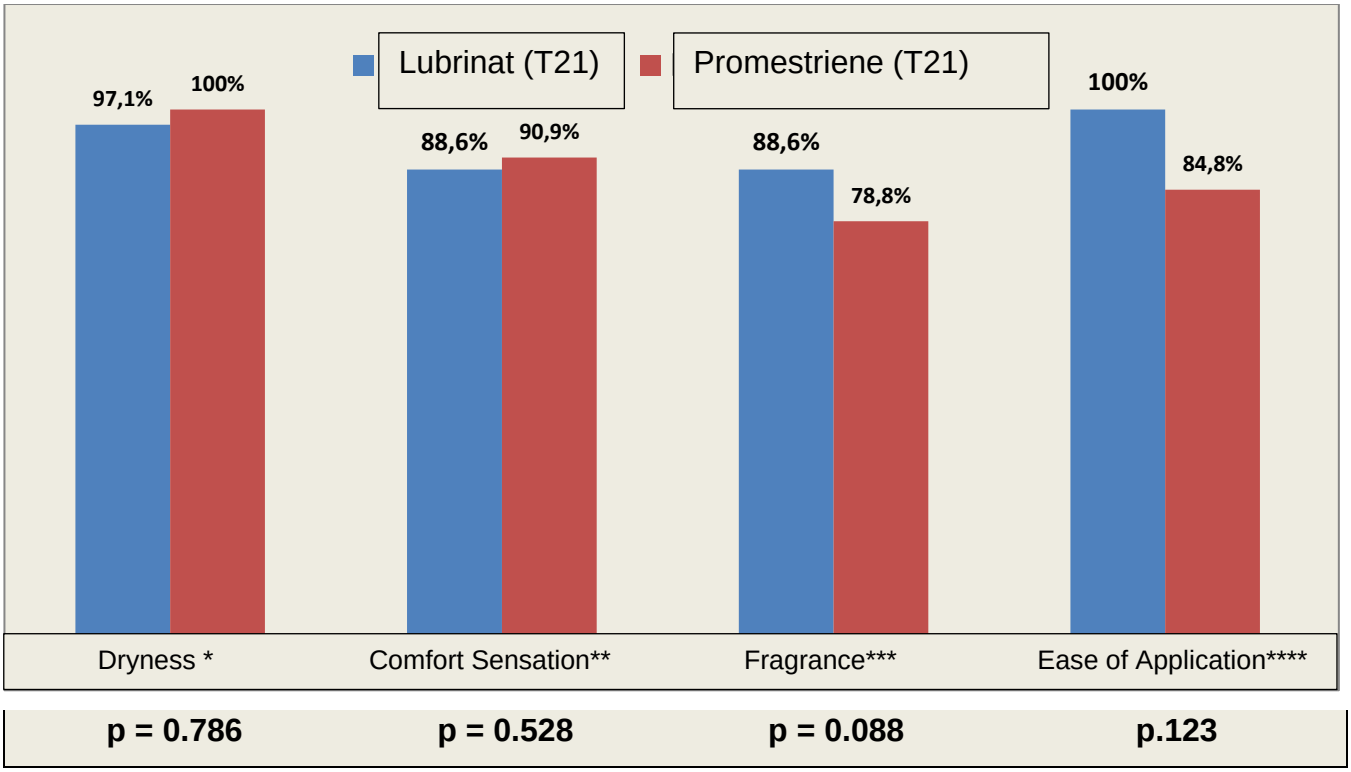
Table II Perceived Efficacy Results

KEY ATTRIBUTES	Lubrinat (T21)	Promestriene (T21)	P Value (1)
Dryness	97 ± 1	100	786
Comfort Sensation **	88.6 (%)	90.9 (%)	528
Fragrance Product ***	88.6 (%)	78.8 (%)	0.088
Ease of Product Application ****	100	84.8 (%)	123

(1) *** significant at the 0.1% level ** significant at the 1% level * significant at 5% (Mann-Whitney test)

For the attribute Dryness, it was considered as the sum of categories " slightly decreased ", "decreased moderately" 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 Product, It was considered as the sum of categories "a little easy ',"easy" and “very easy”.

Figure II: Evaluation of Perceived Efficacy Lubrinat ® vs Promestriene at the end of the study. **(T21)**



For the attribute Dryness, it was considered as the sum of categories " slightly decreased ", "decreased moderately" and "decreased a lot".
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For the attribute Ease of Application Product, It was considered as the sum of categories "a little easy", "'easy" and "very easy".

Conclusion

The etiology of vulvovaginal atrophy at postmenopausal women is associated with the reduction of circulating estrogen resulting in the reduction of skin elasticity and collagen. (1,6-10)

Vaginal atrophy affects the quality of life of postmenopausal women, and observing the orientation of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) in which "Medical assistance to postmenopausal women should be directed to the maintenance of their health, and quality of life and preventive aspects "(11) justifies the search for new therapeutic approaches.

As long as vasomotor symptoms tend to disappear with time, vulvovaginal atrophy tends to worsen continuously (12) 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 maintenance of sexual activity. At the time that vaginal moisturizer does not offer relief, topical estrogen therapy should be applied

considering isolated complaint of vaginal dryness (13). This study: evaluation of the efficacy perceived as therapeutic innovation - Lubrinat® (sodium hyaluronate) supports its use in the initial approach of symptoms of vaginal atrophy.

Table III Summary of conclusions on the evaluation of perceived efficacy Lubrinat® vs Promestriene

✓ 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)

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