CLINICAL STUDY, OPEN, THE CUTANEOUS AND MUCOSA TOLERABILITY OF A TOPIC PRODUCT AND REAL USE CONDITIONS

FINAL REPORT

PRODUCT'S NAME: Lubrinat

PRODUCT CODE: 052818-01

STUDY CODE: All-E-EP-052818-01- 01.10.15

REPORT CODE: AII-S-UG-052818-01-10-15-RFV01-Rev01

DATE OF REPORT: November 17.2015

SPONSOR: MASTER INDUSTRIAL PROD TRADE AND PHARMACIST ODONTO LTDA

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CLINICAL STUDY, OPEN, THE CUTANEOUS AND MUCOSA TOLERABILITY OF A TOPIC PRODUCT AND REAL USE CONDITIONS

SUMMARY

Product's Name :	Lubrinat
Product code:	052818-01
Study Code:	AII-S-UG-052818-01-10-15
Report code:	AII-S-UG-052818-01-10-15-RFV01-Rev 01
PURPOSE OF THE STUDY	Check the skin acceptability of the genital mucosa and perineal region of cosmetic product for topical use by observing the non-occurrence of adverse events and discomfort sensations.
METHODOLOGY	Participants were instructed to use the product at home according to the instructions provided for 21 days (+/- 2 days). They were held evaluations of perceived Efficacy were held, through questionnaires, on the first day of the study, prior to the use of the product (T0) and after 21 days (+ /- 2 days) of use (T21).
PRINCIPLE INVESTIGATOR	Vivian Pessoto Rosa.
PERIOD OF TEST	21 days (+ /- 2 days).
APPLICATION FREQUENCY	Every 3 days.
TEST AREA	Vagina
NUMBER OF PARTICIPANTS	35
POPULATION DESCRIPTION	Female, ages: 42-66 years old, postmenopausal participants and presenting complaint of dryness in the vaginal region.
ETHICS	This study was conducted in accordance with principles of the Declaration of Helsinki, the applicable regulatory requirements, including CNS Resolution No. 466/12, and the Good Clinical Practices (Document of Americas and ICH E6: Good Clinical Practice).
RESULTS	During the study, no participant presented clinical cutaneous signs or in genital mucosa related to the use of the product.
CONCLUSION	The product was considered safe for the evaluated conditions.

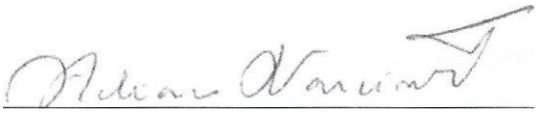
QUALITY ASSURANCE

The study was performed in accordance to CNS Resolution No. 466/2012, in the spirit of the Good Clinical Practice and in accordance with the Allergisa Standard Operating Procedures.

Our quality Data are assured considering that our employees are trained and qualified according the research to be conducted, our equipment are maintained calibrated, and were used recognized and / or validated methods.

The Quality Assurance Area performs audit of the Management System; and is available to receive our customers for specific tutoring of their research.

Representative signature of Quality Assurance System means that the research was conducted as described above.



Quality Manager

Heliara Nascimento Lopes

11/17/2015

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1. LIST OF ABBREVIATIONS

ANVISA	Agencia Nacional de Vigilância Sanitária (Brazilian Health Surveillance Agency)
GCP / ICH	Good Clinical Practice / International Conference on Harmonization.
CNS	Conselho Nacional de Saúde (Brazilian National Health Council)
ICH E6:.	Good Clinical Practice.
T0	Start time, before the use of product test.
T21	Time After 21 days of use of product test.
IC	Informed Consent

2. INTRODUCTION

In the last years, the cosmetic industry has grown considerably as well as its interest in developing effective and safe products. The creation of the Consumer Protection Code, the requirements of the Department of Health Surveillance from the Ministry of Health and the competition itself led to more cautious attitudes from the Industries regarding the action and benefits of their products, seeking to associate their affirmations to the scientific work.

The industry's awareness as well as consumer and regulatory agency requirements have led cosmetics manufacturers to adopt procedures that provide them with better knowledge of their products: they are conducting clinical trials on safety and efficacy coordinated by medical experts before placing their products in the market. These procedures provide companies with more safety, credibility and consumer trust.

Once a cosmetic product is freely available to the consumer, it must be safe under normal or reasonably predictable conditions of use. (According to ANVISA'S Cosmetic Product Safety Assessment Guide).Thereunto, raw materials used in the product formula should be raw materials with proven safety and the use of which is enshrined in the cosmetic industry. Furthermore, the security of final formula should be tested before being placed on the market, as predict the Guide to Cosmetics Safety Evaluation - ANVISA.

According to Good Clinical Practice, adverse event is any untoward medical occurrence that took place in a clinical research participant who has used a pharmaceutical product, but not necessarily presented a causal nexus to the treatment (International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH).

The contact of the skin with topical application of products, such as cosmetics, can cause different kinds of reactions. Among these skin reactions we highlight- contact eczema, urticaria, acne and blemishes (SAMPAIO & RIVITTI, 2000). In general, contact eczema is caused by two mechanisms: by primary irritation, by the action of irritants or sensitization in the presence of some allergenic component.

For assessment of irritant potential and sensitizing of a product, a number of variables must be taken into account: components of the formula, concentration of ingredients, absorption, amount applied, skin condition, mode and frequency application and the cumulative effect (DOOMS-GOOSSENS, 1993).

Skin permeability varies according to the region of the body, with greatest absorption in the folds and face. When a product is applied on the skin, percutaneous absorption is greater or lesser depending on the product's concentration, type of vehicle used, surface skin area and skin contact time (ZATZ,1993). Thus, some regions of the body are more susceptible to irritation than others.

Researches conducted with human beings are regulated according to very rigid laws, in order to protect and safeguard the individuals. These laws vary depending on the country.

In Brazil, these studies are allowed, as long as they follow the precepts of the Declaration of Helsinki and Resolution No 466/12 (CONSELHO NACIONAL DE SAÚDE, 2013).

The research for cosmetics safety assessment aim to confirm the absence of risk associated with the use of the cosmetic product. Compatibility researches carried out through patch test seek to prove the absence of adverse events during application of a cosmetic product for the first time on the skin, thus proving that it is safe for use. Consist of repeated applications of the product on the skin by evaluating the non-occurrence of irritation or sensitization (KLIGMAN & WOODING, 1967; FISHER, 1995). It can be also confirmed the absence of potential photo irritating or photosensitization

On the other hand the researches for acceptability, evaluate the safety of the products in real conditions of use thus enabling to know the product in the same market conditions are conducted with the finished product, prior to its introduction in the market. (BARAN & MAIBACH,1994). In addition to safety, this research can also assess a product's sensory features by identifying additional complaints and comments regarding its performance. Through clinical tests, the company becomes aware of any considerations and complaints that may emerge once its product is sold and may develop strategies, including specific training for the Client Services Center (SAC) prior to product launch (BARAN & MAIBACH, 1994)

3. OBJECTIVE

The objective of this study was to verify the acceptability of a cosmetic product for topical use by observing the non-occurrence of adverse events and skin discomfort sensations of the genital mucosa and the perineal region.

4. INVESTIGATIONAL PRODUCT

The product Information, as declared by the sponsor, is described in Annex 3. A sample of the product was cataloged and is on our files, which will be maintained four a period of one month.

4.1 Identification

Table 1. Product Test Identification

Product Name	Product code
Lubrinat	052818-01

4.2 How to use

Separate urn applicator and open the lid of the tube. To attach the applicator nozzle on the tube screw slowly. After fitting the applicator at horizontal position, gently squeeze the base of the tube with the fingers forcing the gel to enter the applicator, filling it up to the recommended limit. Remove the applicator and close the tube.

The vaginal gel application must be done while lying on your back, deeply introducing the applicator gently into the vagina, Slowly press the plunger until it stops gently pushing the plunger, until completely empty applicator. Apply the product every three days. The gynecological applicator is disposable after use discard.

4.2.1. Compliance check of the Product Use

The compliance check of the product use by the participants was verified through the diary of product use by the participants.

4.3 - Storage

The products supplied by the sponsor were initially stored in the Research Center sample room with temperature controlled and restricted access. The product release was controlled by the principal investigator or designated technicians responsible for it.

Upon receiving the product, the participants were instructed about their storage conditions, highlighting the importance to keep them in places out of reach of children and / or animals.

5. APPLICABLE ETHICAL CONSIDERATIONS

The study was conducted in compliance of the principles of Declaration of Helsinki, the applicable regulatory requirements including CNS Resolution No. 466/12, and in the spirit of the Good Clinical Practice (Document of the Americas and ICH E6: Good Clinical Practice).

Participants were informed of the purpose of the study, its methodology and time, and the benefits expected and possible restrictions related to the study and those who have confirmed their interest in participating signed an informed consent form (Appendix 1).

All the technical documentation of the research is found in the archives of Allergisa, where will be kept for a period of 5 years.

6. STUDY DATES

The total search time was 21 days (+ /- 2 days).

The investigation started on October 19, 2015 and was completed on November 10, 2015.

- **Start:** 10/19/2015;
- **End:** 11/10/2015.

7. RESEARCH PARTICIPANTS

7.1. Recruitment of Research Participants

The recruitment of the research participants was conducted by the recruitment Section at the Research Center, which has a computerized system and updated records. The participants that have an interest in participating in this research are registered in this system who were contacted to participate in the selection and having all the necessary criteria, were included in the study.

7.2. Selection and Admission of Research Participants

During selection of the participants to this research, Allergisa made sure that they had no conditions that could interfere at the results of the study. Allergisa is still responsible for the information present in the participant's Evaluation form, checking all the criteria of inclusion and exclusion for its admission to the research.

7.3. Description of Population

For this study, 36 female participants were recruited to the research between 42 and 66 years old (Annex 2**)**

The study aimed to obtain to its end at least 30 answers, according to Evaluation Guide to Cosmetic Safety the National Sanitary Surveillance Agency Products - ANVISA.

7.4. Inclusion criteria

- Healthy participants;
- Skin and mucosa Integra in the test region;
- Concordance to adhere the procedures and requirements of the test and attend to the Office at the day(s) and hour (s) set for evaluations;
- Capacity to consent participation in the study;
- Females
- Ages: 40-70 years old;
- Menopausal participants;
- Dryness complaint in the vaginal region.

7.5. No Inclusion Criteria

- Cutaneous pathology in the area of product application;
- Diabetes Mellitus Type 1; insulin dependent diabetes; presence of complications due to diabetes (retinopathy, nephropathy, neuropathy); presence dermatosis related to diabetes (ulcer plant, necrobiosis lipoidica, granuloma annular, opportunistic infections); episodes or history of hypoglycemia, diabetic ketoacidosis and / or hyperosmolar coma;
- Immunological deficiency;

- Current use of the following rnedications use of topical or systemic: corticosteroids, immunosuppressant drugs and antihistamines;
- Skin disorders: vitiligo, psoriasis, atopic dermatitis;
- History of Reaction to the category of the product tested;
- Other disorders or medication that may interfere directly in the study or even endanger the health of the research participant.

7.6. Interdiction and restriction

- Do not apply any product in the experimental region to interfere in the study evaluation;
- Do not change cosmetic habits, including hygiene

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8. METHODOLOGY

8.1. Study Design

Open clinical study.

8.2. Study area

Participants were instructed to use the product in the vagina.

8.3. Clinical Gynecologic Evaluation

Participants were evaluated by a gynecologist at baseline (T0) for verification of the criteria for inclusion and exclusion of the study, and at the final visit (T21) to check possible adverse events, discomfort sensations and to confirm the correct use of the product. They were supervised by the gynecologist also throughout the research and evaluated in case of appearance of any symptom or sign, to confirm the correct use of the product and to detect possible adverse events.

Participants were instructed to look for the research coordinator at any time, if they had any complaints. In these cases would be referred for evaluation and guidance of the physician in charge, who would proceed with the examination, the reaction rate and accomplish proper conduct (counseling and or medication and photographic documentation, if necessary).

8.3.1. Adverse Gynecologic Reactions

All reactions would be classified according to their intensity as mild, moderate or intense. If necessary, the product use would be discontinued.

8.4 Procedure schedule

Table 2: Study schedule

		T0	T21
PHASES	Signature of IC	X	-
	Clinical Evaluation by the Gynecologist	X	-
	Efficacy Perceived Evaluation by the Participant Search	-	X
	Acceptability assessment and product conformity by conferring the diaries of use of product test	-	X
	Distribution of the product test	X	-
	Adverse Events Evaluation (if applicable)	-	X

8.5. Criteria and Procedures for Research Participants Withdrawal

The exclusion of research participant by the investigator could be due to the following reasons:

- Research participants not included: participants that signed the informed consent form, but that would not meet the criteria for inclusion and exclusion of the research;
- 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,
- Severe Adverse Event,
- 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.

Participants withdrawn from the study by the investigator will be accompanied if they present any possibly event related to study, even after its withdrawal. Participants will be taken by presenting adverse event will be followed up till the overall solution.
In case of withdrawal after the inclusion phase of the study, there was not reposition of these participants.

9. ADVERSE EVENTS

An adverse event is any untoward medical occurrence that occurred in a patient or participant in clinical research that has used a product, but not necessarily presented a causal relationship to treatment. An adverse event can, therefore, be any unexpected adverse sign(including abnormal laboratory), symptoms, or disease temporally associated with the use of the product test (modified from ICH, 1996).

According to Good Clinical Practice (ICH, 1996), a Severe Adverse Event Record It is any medical occurrence that results in:

- Death;
- Death risk;
- hospitalization or prolongation of existing hospitalization;
- Deficiency/significant or persistent disability;
- Congenital /birth defects.

Any Clinical signs, discomfort sensation, disease, or even clinically significant worsening of these conditions compared to the condition verified at the initial visit is considered an Adverse Event. The lack of clinical efficacy or perceived of a cosmetic product or medicine is not considered an Adverse Event.

Clinical signs and dermatological or systemic diseases have occurred during the process of selection of research participants are not considered Adverse Events. This information is registered at the medical evaluation forms as the reason for non-inclusion and the participants are not included in the research.

Cases of adverse events due to the incorrect use of a cosmetic product or medicine, such as inadequate frequency or incorrect application, adverse events are considered not interfere with product evaluation because the participants did not follow in this situation, the correct guidance for use as used in the labeling thereof.

An Adverse Event Form is completed for all cases of events and these are communicated to the sponsor through an Occurrences release via e-mail or at the final report of the research.

After the appearance of an event with dubious causal nexus, an investigation starts in order to determine whether such an event is or not related to the research and product test.

The procedures adopted during the investigation of the event are defined by the responsible physician based on the nature of the reaction, the participant's medical history and factors that may interfere with the occurrence of the event, as medications or other concomitant diseases.

To conclude the final diagnosis, the relation of an Adverse Event can be defined using the following expressions:

Negative Nexus or Not Related - There is no possibility of a causal link between the product and the adverse event observed.

Unlikely - It is unlikely that there is a positive causal link between the product and the adverse event observed.

Possible – It is possible that there is a positive causal link between the product and the adverse event observed, but there is no way to ensure that.

Likely - it is likely to be a positive causal link between the product and the adverse event observed, although the link is not fully proven.

Positive nexus or certainly related - according to the physician in charge, there is evidence that allow to conclude the causal link as positive between the emergence of the event and the application/use of the cosmetic product or medicine.

10. RESULTS

10.1. Adherence to Study

35 participants completed the study. Of those, 01 had an adverse event (participant 011). The event is described in item 10.2

10.2. Clinical Gynecologic Evaluation

Participant 011

On 11/10/2015, t final date of the research the participant 011 attended the Institute referring burning sensation in the intimate area, of light intensity, immediately after using the product test with duration of seconds and spontaneous remission on 10.19.2015, the first day of the research.

The participant maintained the use of the product-testing until the final date of the research, without recurrence of the complaint.

In the clinical gynecological evaluation it was observed a normal examination without clinical signs.

Considering the picture presented, the case was closed with negative nexus.

The participant data were considered in the research.

During the study, no participant reported discomfort sensations and were not observed clinical signs related to the use of the product.

The data obtained in clinical gynecologic evaluations are listed in Table 3.

Table 3. Clinical Gynecologic Evaluation

PARTICIPANT NUMBER	INITIAL EVALIATUION (T0)	EVALUATION AFTER THE USE OF THE PRODUCT (T21)
001	0	0
004	0	0
006	0	0
007	0	0
008	0	0
011	0	AE
013	0	0
015	0	0
016	0	0
018	0	0
020	0	0
021	0	0
022	0	0
028	0	0
030	0	0
033	0	0
034	0	0
035	0	0
037	0	0
041	0	0
043	0	0
045	0	0
046	0	0
047	0	0
048	0	0
049	0	0
056	0	0
057	0	0
058	0	0
061	0	0
062	0	0
064	0	0
065	0	0
071	0	0
073	0	0

Legend:
AE- = Adverse event negative nexus
SE+ = Adverse event positive nexus
SF = Selection failure after the beginning of the research
W = Withdrawn
0= No reaction
Q =Quitter

11. **CONCLUSION**

According to the methodology used to evaluate the cutaneous acceptability, of genital mucosa and perineal region of **Lubrinat** product forwarded by the company MASTER INDUSTRIA E COMERCIO DE PROD ODONTO E FARMAC LTDA, it can be concluded that:

- During the study, no participant showed clinical signs related to the use of the product.
- The product was considered safe at the evaluated conditions.

Vivian Pessoto Rosa

Principal Investigator

11/17/2015

Dr. Ricardo Barbosa Bueno Campos

Gynecologist CRM 121786

11/17/2015

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ANNEX 3. PRODUCT INFORMATION

Lubrinat

Components
Hyaluronate sodium
Propylene glycol
Natrosol 250 HHX
Sodium lactate, 50% in solution
Sodium benzoate
Lactic acid
Methyl paraben
Cremophor EL
Deionized Water