

CLINICAL TEST AIMED AT EVALUATING THE TOLERABILITY AND SAFETY OF A COSMETIC PRODUCT USED IN THE PERIOCLAR AREA

TORSTONE SA

Le Visage ÉMULSION RÉ-ÉQUILIBRANTE (00733.6)

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STUDY DESIGN

Title

Clinical test aimed at evaluating the tolerability and safety of a cosmetic product used in the periorcular area.

Aim of the study

The test allows to assess whether the tested cosmetic product is tolerated and safe in the eye area. Product safety is tested through the analysis of adverse effects that may occur during the product use (lacrimation, redness, itching, burning).

Eye is a very delicate and vulnerable organ. Many anatomical elements naturally protect it: it is hollow in the eye socket, below frontal bones, and it has a great elasticity to lessen bumps and blunt traumas.

Eyelids represent a defence system too, because they protect the external eye area from foreign bodies and all irritating substances present in the environment. Furthermore, their continuous blinking allows to spread the fluids produced by lacrimal and conjunctival glands on the cornea, with lubricating, bactericidal and detergent functions able to maintain corneal transparency.

Conjunctiva is a mucous membrane covering the back surface of the eyelid and anterior portion of the eyeball: due to its lymphatic component, it is considered a lymph node covered by epithelium, able to react to different types of stimuli. Because of the extreme eye sensitivity to external elements and the stressful conditions which not infrequently is exposed (contact lenses, make-up, sun exposure,...), it is important to pay close attention to this organ reactions, as they may be a symptom of serious damage.

During the study period, the experimenter asks the volunteers about the onset of symptoms such as lacrimation, burning, itching, redness, irritating sensations that occurred after product application. Any adverse reactions towards the product lead to treatment interruption and specific controls, aimed to verify that no eye damages occurred (keratitis, blepharitis, conjunctivitis, chemosis). Here below the main changes that may occur to the eye mucosa:

- **Blepharitis** is an eyelid margin inflammation characterized by redness, swelling, crusts, scales and ulcers. There are two types of blepharitis: ulcerative if it is caused by bacterial infection (staphylococum, almost always) and non-ulcerative (squamous or seborrheic) with unknown causes, usually associated to skin and scalp seborrhoea (dandruff) or of allergic nature. The first manifestation is foreign body sensation, together with lacrimation and light sensitivity. Moreover, it is associated to itching, redness and swelling of eyelid margins.
- **Conjunctivitis** is the most common form of ocular inflammation. The most frequent symptoms are redness, strong lacrimation, mucous or mucopurulent secretion, eyelid swelling, photosensitivity and foreign body sensation. Sometimes conjunctivitis is caused by allergy to substances such as pollen, dust, cosmetics, food, pets such as cat, etc. In addition to the common symptoms, allergic conjunctivitis can be recognized by strong itching and conjunctiva swelling (chemosis), which sometimes is so evident and strong to frighten the patient or his/her family especially due to its sudden onset.
- **Cheratitis** is a cornea inflammation, it causes a lesion of the superficial layer of the cornea with pain, lacrimation, photosensitivity and foreign body sensation.

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Tested Product

Information provided by the Customer

- ✘ Product name:

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- ✘ The tested cosmetic product complies with REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 30th November 2009 on cosmetic products (recast) (Text with EEA relevance) and its annexes.
- ✘ Qualitative INCI formula
Filed

Evaluated parameters

- Product tolerability
- Mucosa and skin alterations

Ethical requirements

The study was carried out in compliance with the following ethical requirements:

- ✘ All subjects participating in the study are healthy volunteers at least 18 years old.
- ✘ All subjects participating in the study are selected under dermatologist's supervision, according to inclusion/non-inclusion criteria (see respective paragraph "Inclusion criteria" and "Non- inclusion Criteria").
- ✘ Volunteer participation in the study is totally free.
- ✘ All subjects participating in the study are informed of the aim and nature of the study.
- ✘ All subjects participating in the study are informed of the potential risks involved.
- ✘ All subjects participating in the study signed their informed consent form at the beginning of the study.
- ✘ Before volunteers were exposed to the product to be tested, all relevant safety information about the product itself and each ingredient were collected and evaluated.
- ✘ All the study procedures are carried out in accordance with the ethical principles for medical research (Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and successive amendments)
- ✘ All necessary precautions were taken in order to avoid any adverse skin reactions.
- ✘ If any unexpected/adverse skin reactions occur, the dermatologist evaluates the severity of the reaction (reporting it on the data collecting sheet) and, if necessary, proceeds with the appropriate therapy.
All the study procedures are carried out in accordance with the ethical principles for medical research (Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and successive amendments)
- ✘ All necessary precautions were taken in order to avoid any adverse skin reactions.
- ✘ If any unexpected/adverse skin reactions occur, the dermatologist evaluates the severity of the reaction (reporting it on the data collecting sheet) and, if necessary, proceeds with the appropriate therapy.

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Subjects selection**Volunteers recruitment**

20 volunteers were recruited in order to take part in the test, in accordance with the following inclusion and non-inclusion criteria:

Inclusion criteria

- Caucasian female subjects
- Age over 18 years
- Healthy subjects
- No eye problems (red eyes, lacrimation, foreign body sensation) that could affect ophthalmologist evaluation
- Commitment not to use other similar products during the study period
- Subjects informed about test purposes

Non-inclusion criteria

- Subjects who do not fit the inclusion criteria
- Pregnant or breastfeeding women
- Subjects with dermatological problems in the test area
- Subjects under pharmacological treatment local/systemic that could interfere with the execution of the test
- Positive anamnesis for atopy (if this condition interferes with the execution of the test)

Withdrawal criteria

The volunteers are withdrawn from the study if

- They do not follow the conditions required on the Study Information Sheet they receive after recruitment
- They suffer any illness, accidents or develop any conditions during the study which could affect the outcome of the study
- They no longer wish to participate in the study.

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Product application method

The product (a cream) has been applied for a month, according to the customer's specifications: "apply on face and eye contour, with movements from the inside to the outside. apply 2 times a day (morning and evening)."

Test execution

Subjects' suitability to take part in the study is evaluated during the first visit, when they receive the product and all the directions about the way of use (daily). Each enrolled subject is instructed to immediately stop the treatment if any unwanted side effects occur and to immediately inform (also by telephone) the specialist about any discomforts that may be attributed to the use of the product itself. Then, the volunteer comes back to our centre after 14 and 28 days of product use, and the specialist evaluates, with volunteer's collaboration, if the product is tolerated and safe for skin and eye mucosa.

Ophthalmologic study evaluations

At each monitored time the experimenter evaluate clinically or with the collaboration of the subject the following parameters:

- Lacrimation
- Vasodilatation (redness, hyperemia)
- Foreign body sensation
- Photophobia
- Itching and/or burning
- Periocular swelling
- Other

The occurrence of these disorders could mean that the product in question is cause of serious alterations of the ocular mucosa such as: conjunctivitis, keratitis, blepharitis, chemosis, oedema and redness on the external eye area. The intensity of each recorded reaction is classified according to a 5 points score:

- absent
- very mild
- mild
- moderate
- severe

and described for its duration, frequency and extension.

The onset of alterations to palpebral skin or ocular mucosa is assessed according to the scores shown in Tables 1-2.

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Global evaluation of the product

The product is ultimately classified as:

- o **Ophthalmologically tested and safe** for its use if none or at most 15% of subjects show a discomfort, related to the application of the product which causes their drop out from the clinical study, in the absence of alteration to conjunctival mucosa and / or eyelid skin.
- o **not tolerated** during its use, if more than 15% of the subjects show a discomfort related to the application of the product which causes their drop out from the clinical study.
- o **not safe** for its use if one or more subjects show an alteration to conjunctival mucosa and / or eyelid skin.

Table 1

Eyelid skin alterations	
No alteration	0
Slight alteration	1
Moderate alteration	2
Evident alteration	3

Table 2

Conjunctival mucosa alterations	
No alteration	0
Slight alteration	1
Moderate alteration	2
Evident alteration	3

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Monitored checks

Volunteers use the product to be tested for 28 days and the evaluations are performed by the experimenter during the first visit (T0) and after 14 (T14) and 28 (T28) days of treatment.

Report change record

The table below reports all the changes made to the document since its initial approval.

Rev. no	Date	Description
0	17/09/19	First release

-
- The results of the study reported in this document only refer to the tested sample and the specific experimental conditions.
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 - A copy of this report is kept on file at Complife Italia s.r.l.
 - Both the informed consent and the information forms are kept on file at Complife Italia s.r.l. for 10 years after the date of issue of the report.

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DEMOGRAPHY

n°	Vol id	Age	Sex	Contact lens wearers	Eyeglass wearers	Sensitive eyes	Sensitive skin	Eyes Colour
1	M2000D	45	F	NO	NO	YES	YES	brown
2	R1927M	57	F	NO	YES	YES	NO	brown
3	G0587G	60	F	NO	YES	NO	NO	brown
4	V2230S	30	F	NO	YES	YES	YES	green
5	M3265G	57	F	NO	YES	NO	YES	green
6	Y4276N	42	F	NO	NO	NO	YES	blue
7	D0668A	53	F	NO	NO	YES	NO	brown
8	V2222D	60	F	NO	NO	NO	NO	brown
9	B4274L	52	F	NO	YES	NO	NO	brown
10	A0004R	46	F	NO	YES	NO	NO	brown
11	S0694M	34	F	NO	NO	YES	YES	brown
12	S0502J	42	F	YES	YES	YES	YES	brown
13	F2070C	58	F	YES	YES	YES	YES	brown
14	I0172A	55	F	YES	YES	YES	YES	blue
15	R1810M	49	F	NO	YES	YES	NO	brown
16	F1926N	46	F	NO	NO	NO	NO	brown
17	C4090C	41	F	NO	NO	YES	YES	brown
18	E4089S	19	F	NO	NO	NO	NO	brown
19	F0122M	47	F	NO	NO	NO	YES	brown
20	P0296C	41	F	YES	YES	YES	YES	brown

RESULTS

TABLE 1

Volunteer no		Lacrimation	Vasodilatation	Foreign body sensation	Photophobia	Itching	Stinging eyes	Periocular swelling	Other
T0									
1	M2000D	0	0	0	0	0	0	0	0
2	R1927M	0	0	0	0	0	0	0	0
3	G0587G	0	0	0	0	0	0	0	0
4	V2230S	0	0	0	0	0	0	0	0
5	M3265G	0	0	0	0	0	0	0	0
6	Y4276N	0	0	0	0	0	0	0	0
7	D0668A	0	0	0	0	0	0	0	0
8	V2222D	0	0	0	0	0	0	0	0
9	B4274L	0	0	0	0	0	0	0	0
10	A0004R	0	0	0	0	0	0	0	0
11	S0694M	0	0	0	0	0	0	0	0
12	S0502J	0	0	0	0	0	0	0	0
13	F2070C	0	0	0	0	0	0	0	0
14	I0172A	0	0	0	0	0	0	0	0
15	R1810M	0	0	0	0	0	0	0	0
16	F1926N	0	0	0	0	0	0	0	0
17	C4090C	0	0	0	0	0	0	0	0
18	E4089S	0	0	0	0	0	0	0	0
19	F0122M	0	0	0	0	0	0	0	0
20	P0296C	0	0	0	0	0	0	0	0

Table 1 summarizes the ophthalmological evaluation at T0 time

TABLE 2

Volunteer no		Lacrimation	Vasodilatation	Foreign body sensation	Photophobia	Itching	Stinging eyes	Periocular swelling	Other
T14									
1	M2000D	0	0	0	0	0	0	0	0
2	R1927M	0	0	0	0	0	0	0	0
3	G0587G	0	0	0	0	0	0	0	0
4	V2230S	0	0	0	0	0	0	0	0
5	M3265G	0	0	0	0	0	0	0	0
6	Y4276N	0	0	0	0	0	0	0	0
7	D0668A	0	0	0	0	0	0	0	0
8	V2222D	0	0	0	0	0	0	0	0
9	B4274L	0	0	0	0	0	0	0	0
10	A0004R	0	0	0	0	0	0	0	0
11	S0694M	0	0	0	0	0	0	0	0
12	S0502J	0	0	0	0	0	0	0	0
13	F2070C	0	0	0	0	0	0	0	0
14	I0172A	0	0	0	0	0	0	0	0
15	R1810M	0	0	0	0	0	0	0	0
16	F1926N	0	0	0	0	0	0	0	0
17	C4090C	0	0	0	0	0	0	0	0
18	E4089S	0	0	0	0	0	0	0	0
19	F0122M	0	0	0	0	0	0	0	0
20	P0296C	0	0	0	0	0	0	0	0

Table 2 summarizes the ophthalmological evaluation at T14 time (after 14 days of product use)

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Volunteer no		Lacrimation	Vasodilatation	Foreign body sensation	Photophobia	Itching	Stinging eyes	Periocular swelling	Other
T28									
1	M2000D	0	0	0	0	0	0	0	0
2	R1927M	0	0	0	0	0	0	0	0
3	G0587G	0	0	0	0	0	0	0	0
4	V2230S	0	0	0	0	0	0	0	0
5	M3265G	0	0	0	0	0	0	0	0
6	Y4276N	0	0	0	0	0	0	0	0
7	D0668A	0	0	0	0	0	0	0	0
8	V2222D	0	0	0	0	0	0	0	0
9	B4274L	0	0	0	0	0	0	0	0
10	A0004R	0	0	0	0	0	0	0	0
11	S0694M	0	0	0	0	0	0	0	0
12	S0502J	0	0	0	0	0	0	0	0
13	F2070C	0	0	0	0	0	0	0	0
14	I0172A	0	0	0	0	0	0	0	0
15	R1810M	0	0	0	0	0	0	0	0
16	F1926N	0	0	0	0	0	0	0	0
17	C4090C	0	0	0	0	0	0	0	0
18	E4089S	0	0	0	0	0	0	0	0
19	F0122M	0	0	0	0	0	0	0	0
20	P0296C	0	0	0	0	0	0	0	0

Table 3 summarizes the ophthalmological evaluation at T28 time (after 28 days of product use)

Table 4 and 5 summarize respectively the alterations of eyelid skin and conjunctival mucosa.

TABLE 4

TABLE 5

ALTERATIONS OF EYELID

Volunteer no	T0	T14	T28
M2000D	0	0	0
R1927M	0	0	0
G0587G	0	0	0
V2230S	0	0	0
M3265G	0	0	0
Y4276N	0	0	0
D0668A	0	0	0
V2222D	0	0	0
B4274L	0	0	0
A0004R	0	0	0
S0694M	0	0	0
S0502J	0	0	0
F2070C	0	0	0
I0172A	0	0	0
R1810M	0	0	0
F1926N	0	0	0
C4090C	0	0	0
E4089S	0	0	0
F0122M	0	0	0
P0296C	0	0	0

ALTERATIONS OF CONJUNCTIVAL MUCOSA

Volunteer no	T0	T14	T28
M2000D	0	0	0
R1927M	0	0	0
G0587G	0	0	0
V2230S	0	0	0
M3265G	0	0	0
Y4276N	0	0	0
D0668A	0	0	0
V2222D	0	0	0
B4274L	0	0	0
A0004R	0	0	0
S0694M	0	0	0
S0502J	0	0	0
F2070C	0	0	0
I0172A	0	0	0
R1810M	0	0	0
F1926N	0	0	0
C4090C	0	0	0
E4089S	0	0	0
F0122M	0	0	0
P0296C	0	0	0

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CONCLUSIONS

According to the previous results, we can conclude that:

TORSTONE SA **Le Visage ÉMULSION RÉ-ÉQUILIBRANTE (00733.6)**

HAS BEEN OPHTHALMOLOGICALLY TESTED. IT IS SAFE TO BE USED IN THE PERIOCLAR AREA

Indeed, no enrolled volunteers showed any significant alterations on their eyelid skin or eye mucosa during the study period.

Experimenter

Dr. Francesco Sandolo

Data analysis and Report

Dr. Carmen Palumbo