LIPOREDUCTYL® CPK

SPECIFICALLY TARGETS ADIPOCYTE MATURATION

CODE: P02-ES600

EFFICIENT PREVENTION, POTENT LIPOLYSIS, LIPOXIDATION BY-PRODUCT CAPTURE AND MICROCIRCULATION ACTIVATION IN ONE PRODUCT!
GENERAL DESCRIPTION

Medically, Cellulite is primarily a condition of poor microcirculation that causes damage to the fat tissue under the skin.

Aesthetically, Cellulite is a problem consisting in the visual presentation of weakened, damaged fatty tissue and fibrous connective tissue in the shape of lumps and dimples, commonly known as “orange skin”.

Cellulite is usually found on the thighs and butt, especially in women. It affects about 80 to 95% of women, regardless of whether they are overweight, average or thin, while it only affects 5% of men due to differences in fat levels and hormonal system. It is a complex process which has several causes of diverse nature: dietetic, vascular, endocrine, lifestyle, etc.

Females have their subcutaneous fat structured in small chambers separated by vertical walls of tissue. The whole framework is irrigated by a complex vascular system of arterioles and capillaries responsible for circulation and drainage.

The failure of this microcirculation system results in leakage of liquid into the surrounding tissue. This liquid retention in the interstitial spaces also affects adipocytes which start manufacturing excess triglycerides and grow in size, becoming trapped in the connective network. This tissue congestion causes swelling, prevents nutrients such as oxygen being carried to the tissue, and hinders the drainage of toxins. A negative cycle starts where enlarged adipocytes pressurize the microcirculation system causing more liquid to leak and more adipocyte growth.

Connective tissue, including collagen and elastin, becomes increasingly damaged; eventually becoming so severely compromised that they scar, causing stretch marks.

The cosmetic result is an uneven distribution of fat and damaged tissue which modifies the appearance of the skin, provoking the well-known lumpy “orange skin” dimples.

A cosmetic treatment against Cellulite must act in two different ways: on the fat (lipolytic effect) and on the circulation (venotonic effect).

LIPOREDUCTYL® CPK is a pro-liposome manufactured as a multi-extrusion composite of classical anticellulite extracts combined with the synergistic effect of a GHK tripeptide. The pro-liposomal formula ensures formation of liposomes once blended into the final preparation. Submicrodispersions are responsible for the homogenous mixture of the actives, and achieve a particle size which favours formation of special liposomes. These special liposomes ensure effective penetration, so transport of the actives to the deepest layers of the epidermis allows effective action on both the lipolytic and venotonic fronts. LIPOREDUCTYL® CPK contains the following actives:

- **CAFFEINE** presents a lipolytic effect: it blocks enzymes responsible for the destruction of AMPc, which is involved in triglyceride breakage. It also possesses
vasodilator properties, increasing blood flow. Therefore, it contributes in both the lipolytic and venotonic effect.

- **BUTCHERBROOM (RUSCUS ACULEATUS) EXTRACT** acts mainly on the microcirculation, decreasing capillary permeability due to its content in a flavonoid called Rutin.

- **IODINE compounds such as TEA-HYDROIODIDE** have effective lipolytic properties by stimulating lipases.

- **IVY (HEDERA HELIX) EXTRACT** contains Hederine, an active saponin responsible for blood vessel protection and permeability decrease. Ivy helps reabsorb the edemas present in the initial stages of cellulite.

- **CARNITINE** is well-known for enhancing triglyceride mobility and accelerating their breakdown.

- **ESCIN** is a venotonic and anti-edematous ingredient.

- **GLYCYL-HISTIDYL-LYSINE** acts as a specific scavenger for certain by-products of lipidic peroxidation such as unsaturated aldehydes. The capture of these by-products increases the effectiveness of the anti-cellulite components.

The combination of all these actives and a special liposomal delivery system capable of penetrating to the lowest levels of the epidermis ensures an effective treatment against Cellulite.

In vitro studies show that LIPOREDUCTYL® CPK has a very specific effect on adipocyte differentiation, since it is a strong inhibitor of the maturation process. LIPOREDUCTYL® CPK acts on the metabolic pathways that lead to the accumulation of lipid droplets inside healthy adipocytes, which means it helps prevent Cellulite, rather than only burning fat once Cellulite has already developed.

LIPOREDUCTYL® CPK’s composition and application are patent pending.
PROPERTIES AND APPLICATIONS

Four specific cellulite-fighting actions:

1. Revolutionary Cellulite prevention due to action on the maturation process of adipocytes
2. Traditional lipolytic activity provided by classic anticellulite extracts
3. Activation of microcirculation due to the powerful venotonic profile of several actives
4. The GHK peptide acts as an efficient scavenger for by-products of lipidic peroxidation

These properties translate into visual effects:
- Enhanced microcirculation improves the skin's complexion
- Improved skin hydration and skin elasticity
- Reduction in thigh and buttock circumference
- Reduction in extracellular water and body fat mass

LIPOREDUCTYL® CPK can be included in creams, lotion, gels, sera, etc, especially in products intended for a preventive anticellulite treatment.

TECHNICAL INFORMATION

PRODUCT SPECIFICATIONS

<table>
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<th>LIPOREDUCTYL® CPK</th>
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<td>Product code</td>
<td>P02-ES600</td>
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<tr>
<td>Appearance</td>
<td>Paste</td>
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<tr>
<td>Colour</td>
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PROCESSING AND DOSAGE

LIPOREDUCTYL® CPK can be incorporated into creams, lotions, gels, sera, etc., at a dosage of 5 – 10% in order to prove effective as an anticellulite treatment.

STORAGE AND SHELF LIFE

LIPOREDUCTYL® CPK should be stored in a clean, dark and cool place. If kept in these conditions shelf life is at least 30 months.

SAFETY

All the raw materials involved in the preparation of LIPOREDUCTYL® CPK have been tested for the evaluation of primary skin irritation potential, sensitisation, ophthalmic irritability, oral and percutaneous toxicity. No signs of irritation, inflammation or allergic reaction were observed at the concentrations of use.
EFFICACY TESTS

“In vitro” tests

CELLULITE PREVENTION: Inhibition of adipocyte maturation and effect on lipid droplet size
A test was carried out on human adipocytes in order to assess LIPOREDUCTYL®’s power as a preventive treatment for Cellulite. An “in vitro” cell culture model of human pre-adipocytes was used, and they were stimulated to differentiate to adipocytes. This was accomplished by using a potent mixture of differentiation agents which induces a strong accumulation of fat inside the lipid droplets contained in the pre-adipocytes. The lipid droplets were visualised by phase contrast microscopy and quantified by image analysis.

During image analysis the following parameters were quantified (average ± SD of duplicate experiments): number of cells per area, number of differentiated adipocytes per area, number of lipid droplets per adipocyte and size of lipid droplets. The results are shown in the following graphs:

Figure 1. Effects of LIPOREDUCTYL® on the number of cells per area

![Number of cells](image)

Fig. 2. Effects of LIPOREDUCTYL® on the number of adipocytes per area

![Number adipocytes](image)

Conclusions: the number of adipocytes decreases whilst the number of total cells is not affected which means LIPOREDUCTYL® targets specifically adipocyte maturation and is not cytotoxic.

Note: the number of cells in the negative control (non-differentiated adipocytes) is higher than in the differentiated cells (either treated with LIPOREDUCTYL® or not) due to the differentiation process which stops proliferation. For the negative control there are no adipocytes, indicating no spontaneous differentiation of pre-adipocytes.
Fig. 3. Lipid droplets (in blue) inside adipocytes

The images show the reduction in adipocytes and consequently in lipid droplets. The decrease is dose dependent. This test confirms the effectiveness of LIPOREDUCTYL® for preventive anticellulite treatments.
SEQUESTERING ACTION: the GHK Tripeptide effectively captures lipid peroxidation by-products

Skin aging is accelerated by processes such as lipid peroxidation. Tissues affected by skin aging contain elevated levels of reactive α,β-unsaturated aldehydes, such as 4-Hydroxy-2-nonenal (HNE), Malondialdehyde (MDA) and Acrolein, all of which are well known by-products of lipid peroxidation.

Lipotec has found, in collaboration with the University of Milan, that the tripeptide GHK is a potent aldehyde-sequestering agent (application under Lipotec patent).

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**Quenching activity of GHK vs HNE**

<table>
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<th>Molar ratio HNE:GHK</th>
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<td>1:15</td>
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**Quenching activity of GHK vs ACROLEIN**

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<td>1:30</td>
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PERCUTANEOUS ABSORPTION STUDIES
A 3D in vitro skin model was used, consisting of pluristratified human keratinocytes, showing morphology and functionality close to that of in vivo human skin. Under the artificial epidermis there is a semipermeable membrane in communication with the underlying compartment which contains the culture medium (undernatant). The skin model is Skinethic® (Skinethic Laboratories, Nice).

LIPOREDUCTYL (200 mg) was added to each epidermal unit, the quantities of caffeine and escin in the formula having been previously determined. Pure caffeine was diluted to 20 ppm in the culture medium and 200 µL were placed in contact with the skin model. Pure escin was diluted to 50 ppm in the culture medium and 200 µL were placed in contact with the skin model.

After 2, 4 and 16 h an amount of 200 µL of undernatant was collected from each well to evaluate caffeine and escin absorption. The samples were weighed and analysed by HPLC.
Conclusions: LIPOREDUCTYL’s liposomal formulation favours epidermal penetration, as demonstrated by the fact that caffeine penetration is increased almost 5 fold compared to pure caffeine and escin penetration is increased up to almost 8 fold. The encapsulation of the actives in liposomes also enables a slow release, as proved by determinations at 16 hours, where caffeine is absorbed 3 times more than pure caffeine and escin reaches its maximum absorption of almost 4% (7.7 times more than pure escin).
“In vivo” tests

Evaluation of the anticellulite effects on the skin of LIPOREDUCTYL®.
The global action of LIPOREDUCTYL® as an effective anticellulite was evaluated in a study performed on 20 females with cellulite imperfections, aged between 18 and 70. The product (containing 7% of LIPOREDUCTYL®) was applied daily for 60 days on specific body areas (Glute SX, Glute DX, Femoris Post SX, Femoris Post DX, Femoris Ant SX, Femoris Ant DX) and the following parameters were studied:

| Instrumental measurement | • circumference of buttocks and thighs  
|                          | • body fat mass*  
|                          | • extracellular water*  
|                          | • skin moisture**  
|                          | • elasticity***  

Measurement performed by:
• STA/BIA instrument*  
• Corneometer**  
• Cutometer***  
All instruments are authorised according to EU regulations.

| Subjective evaluation (by dermatologist) | • microcirculation  
|                                         | • orange skin  
|                                         | • presence of nodules  
|                                         | • skin smoothness  
|                                         | • skin compactness  
|                                         | • complexion  

A score between 1 – 4 is given to the dermatologist’s evaluation. A Frideman test is used for the statistical analysis of non parametric data (Cosmetic News, 130, 30 – 32).

| Video Capillaroscopy | Images of the skin were taken, before and after the test, using Video-Capillaroscopy which achieves 200 X magnifications of cellulite imperfections allowing the study of microcirculation, etc. This technique makes it possible to study:  
|                       | -Fracture of the polygonal net  
|                       | -Capillary splitting  
|                       | -Apical microaneurysms of ansae  

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Instrumental measurements

Buttock circumference

Cms

Day 0
Day 60

15% of patients showed a very significant decrease of 2.0 to 3.0 cms while 60% showed a significant decrease of 0.5 to 1.0 cms.

Thigh circumference

Cms

Day 0
Day 60

85% of patients presented a significant decrease of 0.5 to 1.0 cms.

Average Extracellular Water (ECW)

ECW (litres)

Day 0
Day 60

60% of patients show a very significant decrease of 0.5 to 1.6 litres

Body Fat Mass

FM (kg)

Day 0
Day 60

50% of the patients show a significant decrease of 0.6 to 1.4 kgs

Skin Elasticity

Elasticity (Cutometer reading)

Day 0
Day 15
Day 30
Day 60

After Day 30, the increase was 17.5% and after Day 60 it was 24.4%.

Skin Hydration

Skin hydration (Cornemeter readings)

Day 0
Day 15
Day 30
Day 60

After the treatment, the moisturising index had increased by 9.5%. 
The polygonal net is more regular in 60% of patients after the test. Another 35% had a slight improvement. 75% of patients presented an improvement in orange skin, one third of those presented a fairly good improvement.

In 95% of patients, nodules condition has improved, and both micronodules and macronodules seem less evident. 40% experienced a fairly good improvement. 65% of the patients finished the test with smooth skin.

There is a significant variation of skin compactness from the 30th day of treatment which is an index of improved cutaneous trophism. After the treatment, 55% of volunteers show a compact and elastic skin. After the treatment, 65% of the patients show a rosy complexion which is a sign of improved microcirculation.
CONCLUSIONS:

- All pictures show an improvement in the structure of microcapillaries and a decrease in microhaemorrhages.
- The macroscopic translation is a rosier complexion, less evident presence of nodules and an improvement in the degree of orange skin.
# GENERAL PRODUCT INFORMATION

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## INGREDIENTS

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<sup>a</sup> Not Listed

Note: due to the natural origin of some ingredients in Liporeductyl®, differences in colour may appear between batches. We recommend the use of Caramel (INCI: CARAMEL), a natural dye, to be added for colour adjustment (between 0.001% to 0.02%)

Note: Graphs and photographs are available for customer use provided that the final product contains the same concentration of active as the formulations in our tests. Customers must request written permission for use of the graphic material and/or ingredient tradenames to Lipotec. Customers are responsible for compliance with local and international advertising regulations.

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