Technical Report

Product

NOCTURSHAPE™

blue ingredient

Date

January 2016

Revision

1

Lipotec
A Lubrizol Company

Pol. Ind. Camí Ral C/ Isaac Peral, 17
08850 Gavà Barcelona (Spain)
Tel. +34 93 638 80 00
www.lipotec.com
commercial@lipotec.com

Contents

Synchronized biological processes for wellbeing

Biological processes in living organisms are subjected to a **cyclic temporal organization**. This organization allows the regulation of various physiological and behavioral processes so that they take place at the right time and repeat with the appropriate frequency (e.g. daily, monthly, yearly).

The most relevant of biological cycles are **circadian rhythms**, which comprise the oscillations that recur with a period of approximately 24 hours. The term circadian comes from the Latin phrase *circa diem*, which means 'about a day'. The sleep-wakefulness cycle and the changes in body temperature are examples of circadian rhythms. Body temperature, for instance, decreases at night and rises during the last hours of sleep [1].

The circadian organization of biological functions provides an optimal **adaptation of the organism to the recurrent variations in the environment**. So, it ensures the preparation of the organism for the upcoming changes associated with day-night cyclicity due to Earth rotation, such as light-darkness or the availability of nutrients. In addition, it affords an internal temporal organization so that biological processes take place in coordination with one another. Synchrony of the organism with both its external and internal environments is **critical to health and well-being** [2].

Circadian desynchronization occurs when biological and social times are misaligned. This is a widespread phenomenon in contemporary lifestyles, where artificial lighting and alarm clocks allow extended schedules and night work. In addition, there is frequently a significant displacement between workday and weekend schedules and jet lag caused by transmeridian traveling is not uncommon. These altered relationships between biological and social time, known as **'social jet lag'**, can cause among other disturbances sleep restriction and unnatural patterns of food consumption that can impair job performance and wellbeing. Additionally, long-term circadian desynchrony has **negative consequences for human health** and can lead to undesired physical changes that affect **corporal appearance**, including overweight [3].

Contemporary lifestyles are increasingly characterized by 'social jet lag' and its negative consequences, together with a reduced availability of time for exercising and personal care. This is raising the **need for more efficient cosmetic ingredients** that help save time and accommodate to the new necessities while taking into consideration the importance of circadian rhythms.

Maintaining a good synchronization of circadian rhythms is essential for health and wellbeing.

Clock genes and the internal biological clock

All the circadian processes in the body are regulated by an **internal biological clock** that receives external signals and maintains the synchronization with the 24-hour period. The major external synchronizing signal is **light**.

The central biological clock, which resides in the brain's **suprachiasmatic nucleus (SCN)**, receives light signs from the retina. After integrating light information and other signals, the SCN coordinates, through neuronal and hormonal signals, the **peripheral clocks located in different tissues and organs** throughout the body, to trigger circadian rhythms. Light-induced activation of the SCN prevents the production of the hormone melatonin in the brain. **Melatonin** indicates 'biological night' to the body and is one of the outputs of the central clock that distributes temporal signs to peripheral tissues [2].

Both central and peripheral clocks are governed by the same molecular mechanism, which is composed of **clock genes**. The main clock genes are *CLOCK*, *BMAL1*, *PER* and *CRY*. These genes control their own expression and, in addition, coordinate the timing of expression of downstream effector genes, known as **'clock-controlled genes' (*CCGs*)**. These have precise cellular functions and are responsible for the rhythmic execution of circadian processes in each tissue [4, 5].

The activity of clock genes oscillates along a 24-hour period, forming a **network of regulatory feedback loops**. In the morning CLOCK/BMAL1 protein heterodimers activate the expression of *CCGs* and of clock genes *PER* and *CRY*, leading to an increase in their protein levels along the day. At night, PER/CRY protein complexes inhibit CLOCK/BMAL1 activity in the nucleus, suppressing the expression of further *PER* and *CRY* genes. The next morning, PER and CRY protein levels have decreased and no longer inhibit their own transcription by CLOCK/BMAL1, restarting the cycle. The changing levels of activation and inhibition of the various *CCGs* through the cycle determines the execution of the different rhythmic outputs [4, 5].

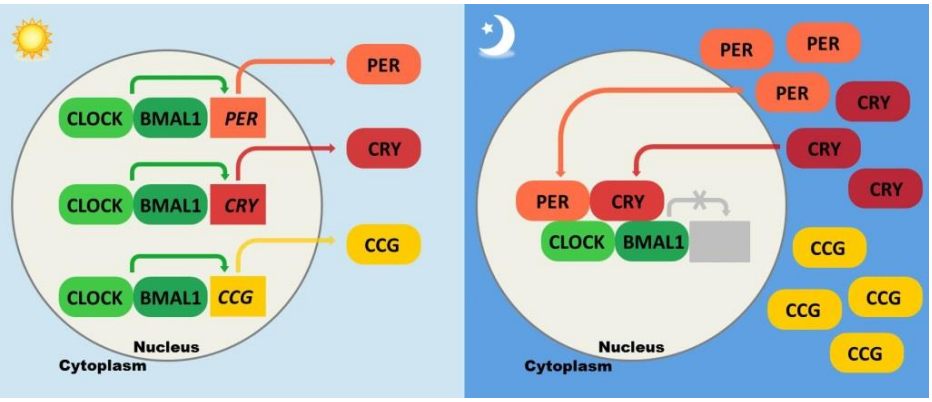


Fig. 1. Schematic view of the regulation of the biological clock by clock genes.

Circadian rhythms are synchronized to external signals and governed by an internal biological clock that consists of an array of clock genes and proteins.

Application of chronobiology to solve cosmetic concerns

The majority of cells and tissues of the body contain clock genes and thus may modulate their activity on a 24-hour rhythm basis [1, 5]. Over the years, evidence of the relevance of circadian rhythms in the treatment of various diseases has increased. Accordingly, **chronobiological parameters** are being used **in pharmacological studies** for assessing the right time for the administration of drugs and for the observation of their effects [6].

Similarly, it is essential to take into account the importance of circadian rhythms when **developing and testing cosmetics**. Thus, it can be considered what could be the best time for the application of a product, so that it will better reach the cells or tissues of interest. It is also important to understand the biological rhythms of the tissue and of the molecular mechanisms that are going to be addressed by an active ingredient in order to achieve more efficient results.

Among the tissues that exhibit circadian patterns, the skin and adipose tissue are the most relevant in cosmetics. The circadian variations in skin parameters is important to determine for instance the best time of the day for the application of a particular cosmetic ingredient.

Adipose tissue functions follow various biological rhythms in processes such as adipogenesis (adipocyte maturation from precursor cells), lipogenesis and lipolysis (lipid synthesis and degradation respectively). The circadian clock of this tissue is synchronized to the 24-hour cycle via neuronal and hormonal inputs and tightly controls those processes through transcription rhythms and the control of key proteins [5, 8].

Adipocyte differentiation is regulated by clock genes, and some genes that enhance the process increase their expression at night, promoting the maturation of adipocytes [9]. Growth hormone is naturally released during nighttime and activates **lipolysis** in adipose tissue and blood flow [10]. Likewise, the clinostatic position during sleep facilitates draining of liquids. So, circadian rhythms can be relevant for the identification of circadian-regulated molecular components involved in the development of cosmetic problems such as cellulite as well as knowing when to apply cosmetic treatments.

Circadian rhythms need to be considered to more efficiently deal with various cosmetic concerns.

Nocturnin: a circadian protein in adipogenesis control

Originating in subcutaneous adipose tissue, cellulite is an aesthetical displeasing condition that approximately 90% of post-adolescent women experience in some degree [11]. Together with well-known factors like hormone imbalances, overweight, poor diet or physical activity, and smoking, the appearance of cellulite could be influenced by circadian rhythms of the body [12].

Cellulite is characterized by the unevenness of the skin's surface relief, known as 'orange peel' or 'cottage cheese' appearance, occurring mainly in the thighs, hips, buttocks and stomach areas. Excessive adipose tissue deposits develop because of **adipogenesis and the enlarged size of adipocytes** caused by lipid accumulation. Besides, due to a rise of collagen breakdown and a decrease of elastic fibers, **connective tissue becomes thinner and weakened**, allowing adipocytes to move towards the surface of the skin to form cellulite characteristic fat nodules. In addition, microcirculatory alterations and fluid retention worsen and sustain cellulite development [11, 12].

Adipogenesis is regulated by a series of signaling cascades that involve circadian genes and proteins. **Nocturnin is a circadian *CCG* that controls adipogenesis** in adipose tissue. Its levels oscillate daily, with a peak occurring at the start of the dark cycle (evening) [13]. Nocturnin protein is upregulated in early adipogenesis and is necessary for the stimulation of their differentiation to mature adipocytes [9, 13].

Nocturnin controls adipogenesis and lipid metabolism through the **modulation of the activity of peroxisome proliferator-activated receptor γ (PPARγ)**, which is key transcription factor in the adipogenesis process. The expression of PPARγ is increased with age, and seems to be related to the higher accumulation of fat associated with the aging process [14]. Nocturnin directly binds to PPARγ enhancing its nuclear translocation and thus its transcriptional activity, which results in increased adipogenesis and incorporation of lipids into adipocytes [13].

The fact that nocturnin promotes adipogenesis and fat accumulation and it has a circadian cycle of expression makes of this protein an interesting target for fighting fat accumulation. Thus, the application of cosmetic ingredients that modulate the activity of nocturnin at nighttime is a promising anti-cellulite strategy.

Nocturnin is a circadian protein involved in adipogenesis and lipid accumulation at night.

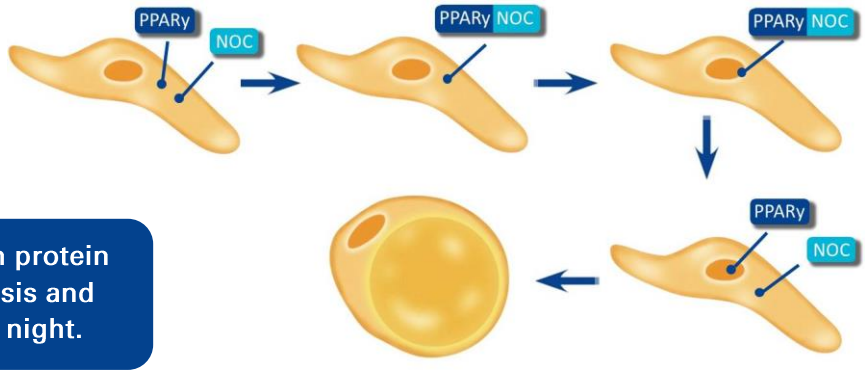


Fig.2. Nocturnin protein (NOC) regulates the nuclear translocation of PPARγ.

NOCTURSHAPE™ *blue ingredient* targets *n*octurnin for a more slender silhouette

NOCTURSHAPE™ *blue ingredient* is a biotechnological active that reduces nocturnin levels, and thus diminishes the subcutaneous fat deposits of cellulite. It is an **exopolysaccharide (EPS)** produced by fermentation of a planktonic microorganism (*Halomonas sp.)* that was isolated in **Fuente de Piedra Lagoon** (Málaga, Spain). The shallow waters of this lagoon have a high salt concentration that determines the presence of abundant microscopic organisms, and constitute a strategic point for migrating birds, remarkably hosting a large population of elegant pink flamingos.

NOCTURSHAPE™ *blue ingredient* has been designed to obtain a superior anti-cellulite benefit by **taking advantage of the circadian rhythms** of the body. The biotechnological ingredient can be used in a single daily application at nighttime, to act specifically when nocturnin is more active.

In vitro NOCTURSHAPE™ *blue ingredient* reduced nocturnin protein levels in synchronized adipocytes. It proved to **induce lipolysis** and significantly **reduced lipid accumulation** in adipocytes. Besides, it **increased type I collagen** levels in dermal fibroblasts, which is expected to reinforce the dermal matrix of the skin.

In a clinical test, the ingredient clearly **improved the different signs of cellulite** in female volunteers that applied a formulation at nighttime. Hence, NOCTURSHAPE™ *blue ingredient* reduced thigh contours while smoothening the skin relief and increasing the uniformity of subcutaneous fat. In addition it provided a firming effect and a general improvement of skin appearance.

Fig.3. Fuente de Piedra Lagoon in Málaga (Spain).

NOCTURSHAPE™ *blue ingredient* greatly reduces fat and smoothes the skin by modulating nocturnin.

In vitro efficacy

REDUCTION OF NOCTURNIN PROTEIN LEVELS

The ability of the ingredient to reduce nocturnin protein levels during the night was tested. Human subcutaneous preadipocytes were synchronized to a day-night rhythm during differentiation in preadipocyte differentiation medium 2 (PDM2). Day-night synchronization was achieved by alternating 12 h incubations in PDM2 alone (induced day) with 12 h incubations in PDM2 with 1 nM melatonin (induced night) for 4 consecutive days.

After 4 day-night cycles, the cells were maintained for 6 h under induced day or induced night conditions and nocturnin protein levels were assessed to confirm the differential expression of nocturnin between day and night.

Synchronized cells were treated with 0.1 mg/mL of NOCTURSHAPE™ *blue ingredient concentrate* for 6 h under induced night conditions.

Intracellular nocturnin protein levels were quantified using an enzyme-linked immunosorbent assay (ELISA). In parallel, total protein concentrations were obtained by the bicinchoninic acid (BCA) assay. ELISA data were normalized by total protein concentration and the relative nocturnin protein levels were calculated.

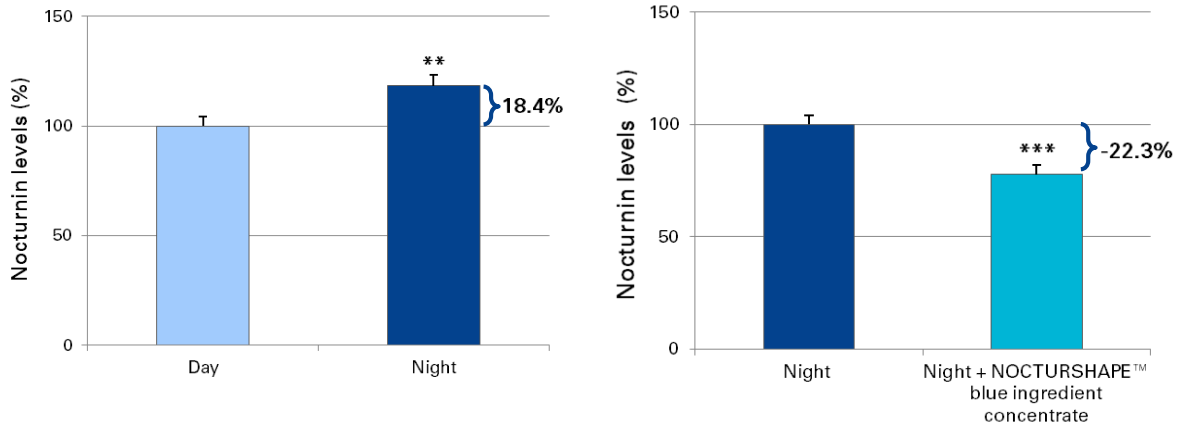


Fig. 4. Nocturnin levels in synchronized adipocytes and the effect of NOCTURSHAPE™ *blue ingredient* at night (**p<0.01; *** p<0.001).

Synchronized adipocytes under induced night showed significantly higher nocturnin levels compared with adipocytes in induced day. The EPS significantly **decreased nocturnin protein levels (22.3%)**.

NOCTURSHAPE™ *blue ingredient* reduces the levels of the circadian protein nocturnin in adipocytes.

INDUCTION OF LIPOLYSIS AT NIGHT

Lipid mobilization from adipocytes involves hydrolysis of triglycerides into glycerol and free fatty acids. Therefore, the release of glycerol by the adipocytes was measured to assess the ability of the ingredient to induce lipolysis.

Human subcutaneous preadipocytes were differentiated for 6 days and later synchronized for 4 day-night cycles. Then the cells in induced night conditions (with melatonin) were treated with 0.1 or 1.0 mg/mL NOCTURSHAPE™ *blue ingredient concentrate* or left with no treatment (control) for 6 h.

Glycerol levels in the cell supernatants were quantified by fluorometry, using a Free Glycerol Assay kit, and normalized by total protein concentration, determined by BCA.

Additionally the lipid droplet content in the cells after the different treatments was observed using a bright-field microscope.

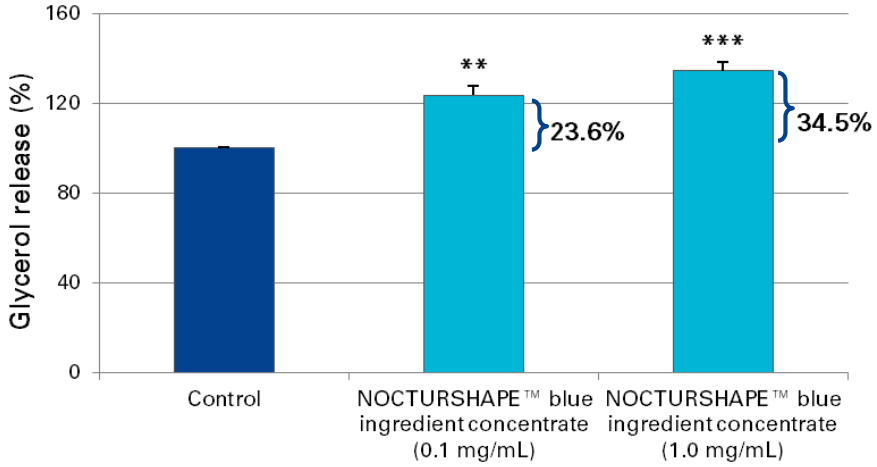
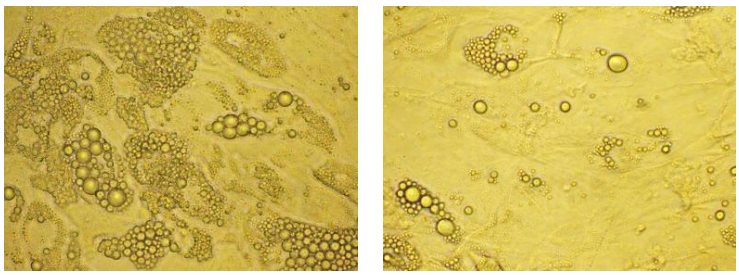


Fig. 5. Free glycerol release in synchronized adipocytes during the night (** p< 0.01, ***p<0.001).



Control

NOCTURSHAPE™ *blue ingredient concentrate* (1.0 mg/mL)

Fig. 6. Microscopy images showing the reduction of lipid droplets caused by the EPS.

The **release of glycerol** increased significantly (by 34.5%) after the treatment with the EPS.

NOCTURSHAPE™ *blue ingredient* induces lipolysis in adipocytes at night.

DECREASE OF LIPID ACCUMULATION

The ability of the active to reduce the storage of lipids was assessed. Human subcutaneous preadipocytes were induced to differentiate in PDM2 alone (differentiated cells) or in the presence of 0.1 or 0.01 mg/mL of NOCTURSHAPE™ *blue ingredient concentrate* for 8 days. As a positive control of inhibition of lipid accumulation, the cells were treated with 0.2 mg/mL caffeine. Non-differentiated cells were used as a control.

Nile Red staining (Adipored™ reagent) was used for the quantification, by fluorescence, of intracellular lipids. The signal of each condition was corrected with the mean fluorescence value of the non-differentiated cells and normalized by the result of the differentiated cells.

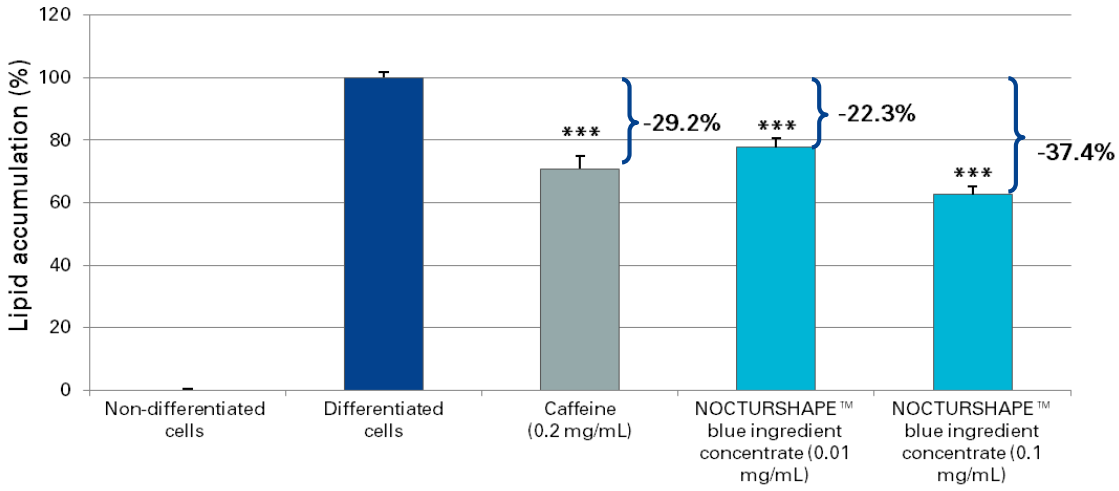


Fig. 7. Lipid accumulation in human adipocytes (*** p<0.001).

The EPS significantly **decreased lipid accumulation** in human adipocytes. The effect was dose-dependent and reached a **37.4%** decrease.

NOCTURSHAPE™ *blue ingredient* is more effective than caffeine in reducing lipid accumulation.

TYPE I COLLAGEN INDUCTION

The induction of type I collagen by the EPS in dermal fibroblasts was evaluated.

Human dermal fibroblasts from adult (HDFa) were treated with 5 or 10 µg/mL NOCTURSHAPE™ *blue ingredient concentrate*. Non-treated cells were used as the control. After 48 h of incubation, the fibroblasts media were collected.

The concentration of type I collagen in the media from HDFa was evaluated by ELISA. Collagen concentrations were obtained using the standard curve and the percentage of induction with respect to control was calculated.

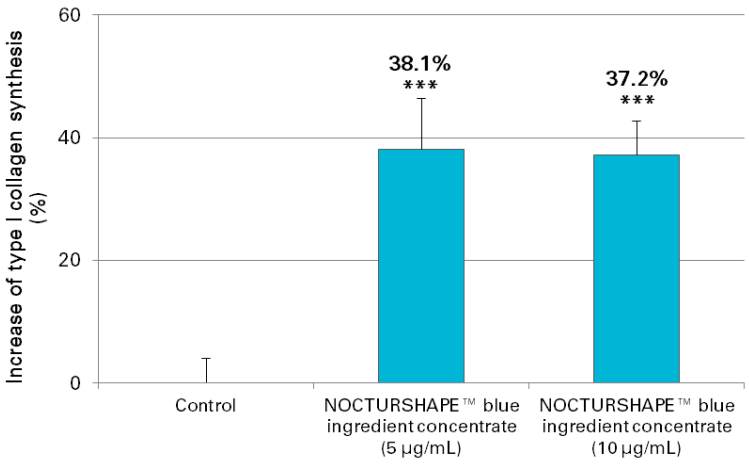


Fig. 8.Type I collagen synthesis in HDFa (*** p<0.001).

The EPS showed a positive effect on **type I collagen synthesis** in HDFa. It induced collagen I expression **by 38.1%**, possibly contributing to increase skin firmness.

NOCTURSHAPE™ *blue ingredient* enhances the expression of collagen I in dermal fibroblasts.

In vivo efficacy

IMPROVEMENT OF CELLULITE APPEARANCE

To test the efficacy of NOCTURSHAPE™ *blue ingredient* to reduce, firm and improve the appearance of the skin, a test was performed on volunteers with cellulite grades II and III of Nurnberger-Muller scale.

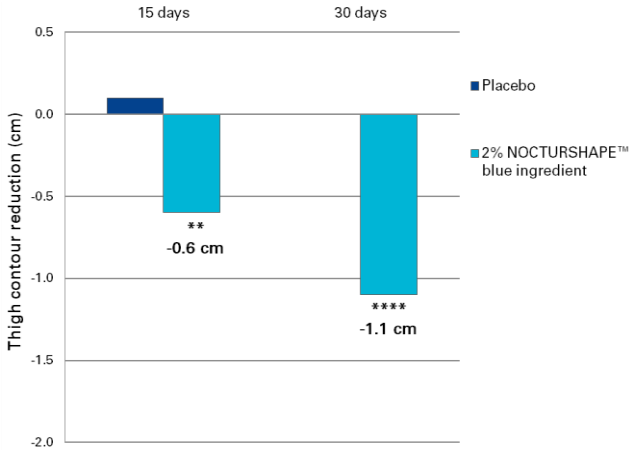
A panel of 21 female subjects between 27-45 years old applied a cream with 2% NOCTURSHAPE™ *blue ingredient* or a placebo cream.

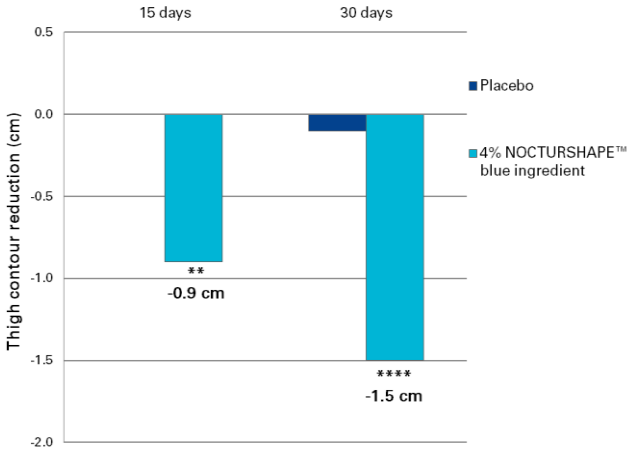
A second panel with 20 female subjects between 25-47 years old applied a cream with 4% NOCTURSHAPE™ *blue ingredient* or a placebo cream.

Each subject applied the cream with NOCTURSHAPE™ *blue ingredient* on one side (left or right) of the body and the placebo cream on the other side. The volunteers applied the formulations once daily at night, in the area of the hips and thighs. Efficacy assessments were made before the treatment and after 15 and 30 days.

REDUCTION OF THIGH CONTOURS

Digital photos of the subjects were taken and the meanthigh circumference (between the high and mid-thigh) was obtained using image analysis software. Finally, the mean reduction in thigh circumference with respect to the measurement before the treatment was calculated.





NOCTURSHAPE™ *blue ingredient* **reduced** thigh contours **up to 1.5 cm after 15 days** and **up to 2.1 cm after 30 days** of treatment at 4%.

NOCTURSHAPE™ *blue ingredient* reduced thigh contours on average by 0.9 cm after 15 days.

SMOOTHENING OF THE SKIN RELIEF

Digital photographs of the subjects were taken and analyzed to determine the improvement in the skin relief skin parameter with respect to the baseline condition.

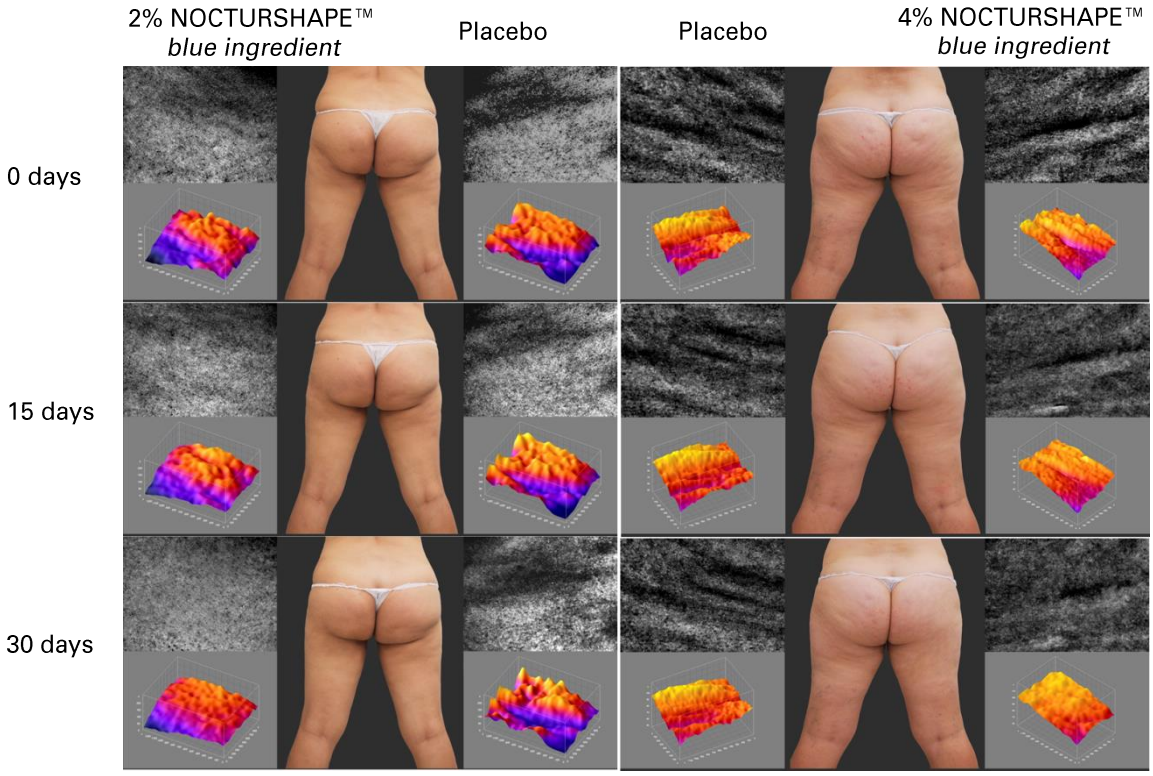


Fig. 10. Images and depth-coded maps of skin surface relief.

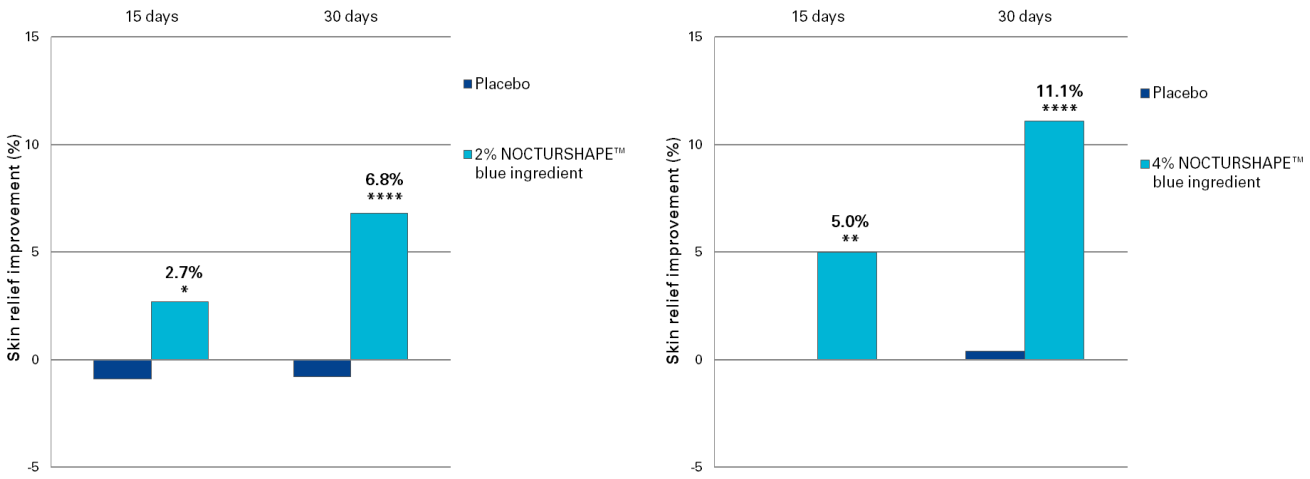


Fig. 11. Improvement in the skin relief (*p<0.05; **p<0.01; ****p<0.0001).

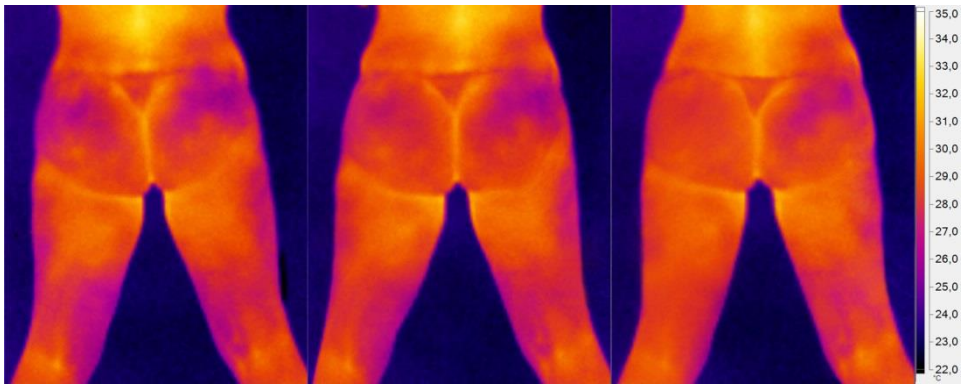
The side treated with the active ingredient displayed a significant **improvement of skin relief**. After 30 days of treatment the skin was 6.8% (at 2%) and **11.1%** (at 4%) smoother.

NOCTURSHAPE™ *blue ingredient* significantly smoothened the skin relief.

THERMOGRAPHIC ASSESSMENT OF FAT EVENNESS

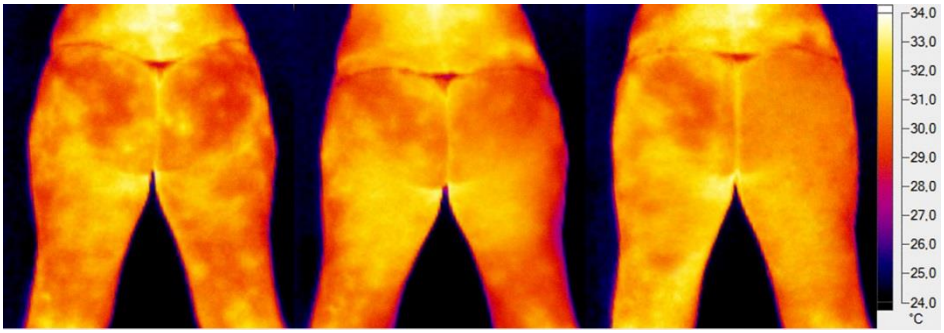
Subcutaneous fat hinders, by thermal insulation, the outwards transfer of heat from the circulatory system. The uneven build-up of fat deposits of cellulite leads to a heterogeneous distribution of the temperature that is irradiated to the skin surface.

After 30 minutes resting in a climate-controlled environment, infrared thermographic images of the area of the buttocks and back of the thighs were taken using a thermographic camera. The images obtained were analyzed using a software program to obtain the mean variation of temperature within the skin. Finally, the uniformity of the skin surface temperature was calculated, as it as it indicates the degree of improvement of cellulite with respect to the baseline conditions.



0 days 15 days 30 days

Fig. 12. Thermographic images of a subject that applied a cream with 2% NOCTURSHAPE™ *blue ingredient* on the left side and a placebo cream on the right side.



0 days 15 days 30 days

Fig. 13. Thermographic images of a subject that applied a placebo cream on the left side and a cream with 4% NOCTURSHAPE™ *blue ingredient* on the right side.

After 30 days, the **homogeneity of skin temperature improved by 29.5% and 39.4%** with the application of 2% and 4% of the EPS respectively. The results of the active ingredient were significantly better than those of placebo.

NOCTURSHAPE™ *blue ingredient* increases the uniformity of skin temperature, showing a better microcirculation and a reduction of uneven fat build-up.

ASSESSMENT OF SKIN FIRMNESS

Skin firmness was measured by cutometry on thighs before the treatment and after 15 and 30 days. The parameter relating to skin firmness, Uf, was obtained and the improvement in skin firmness with respect to baseline conditions was calculated for each treatment.

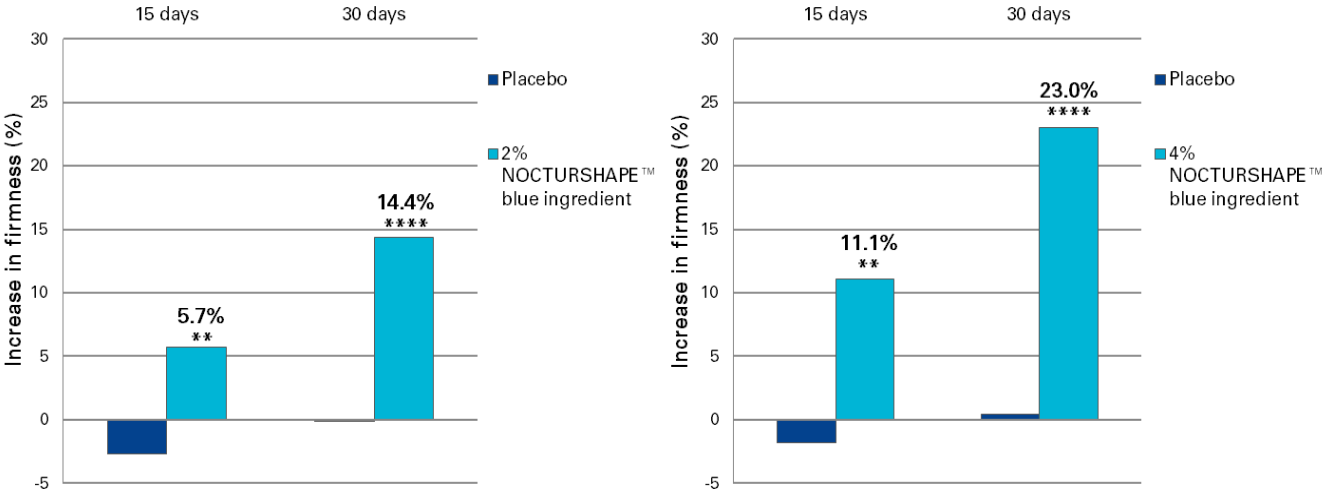


Fig. 14. Improvement of skin firmness (**p<0.01; ****p<0.0001).

The side treated with 4% of the active cream displayed a significant **improvement in skin firmness** after 15 days (**11.1%**) and 30 days (**23.0%**) of treatment.

Treatment with NOCTURSHAPE™ *blue ingredient* induces a firming effect on thighs.

SENSORY ASSESSMENT OF CELLULITE APPEARANCE

A clinical evaluation on the signs of cellulite was performed by the researcher by giving a score for the intensity of cellulite. The improvement in skin aspect after 15 and 30 days was calculated from the scores to evaluate the general reduction of signs of cellulite.

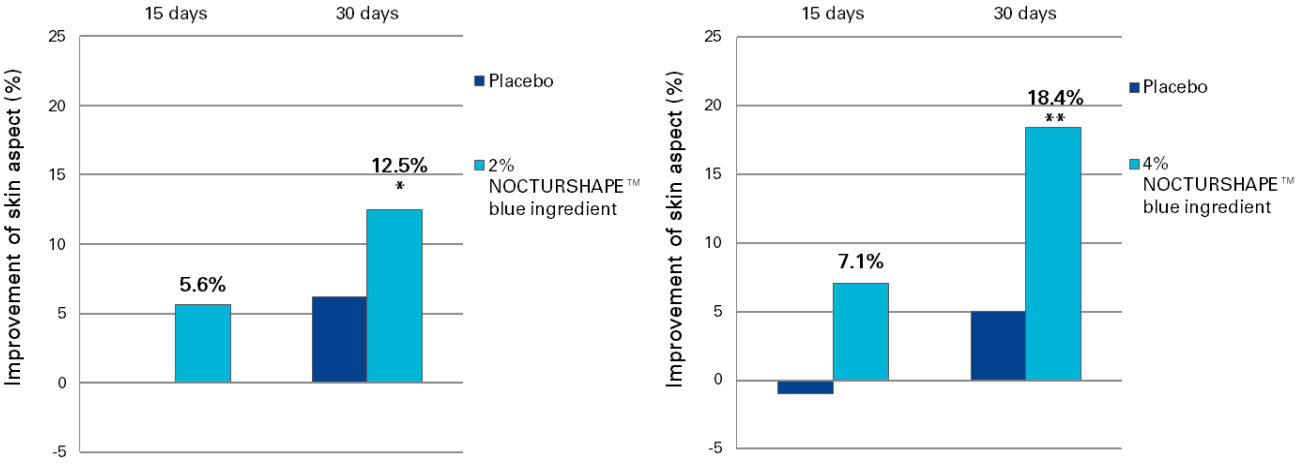


Fig. 15. Enhancement of the skin aspect (*p<0.05; ***p<0.01).

The sides treated with 2% and 4% NOCTURSHAPE™ *blue ingredient* improved their appearance by **12.5% and 18.4%** respectively after 30 days, indicating an **enhanced aspect of the skin**. The results of the active ingredient were significantly better than those of placebo.

NOCTURSHAPE™ *blue ingredient* provides a general improvement in the aspect of the skin.

Cosmetic properties

anti-cellulite slimming

NOCTURSHAPE™ *blue ingredient*:

- EPS from Fuente de Piedra Lagoon (Málaga, Spain) that **decreases the levels of the circadian protein nocturnin**, involved in adipogenesis and lipid accumulation at night.
- reduced by **22.5%** the protein levels of nocturnin in synchronized adipocytes **during the night**.
- enhanced **lipolysis by 34.5%** in synchronized adipocytes and **decreased lipid storage by 37.4%**.
- induced the expression of **type I collagen** by dermal fibroblasts **by 38.1%**.
- applied at night for 15 days, 4% NOCTURSHAPE™ *blue ingredient* **reduced thigh contour almost 1 cm**.
- **smoothened the skin relief** by **11.1%** and **reduced the unevenness** of subcutaneous fat deposits by **39.4%**, after 30 days (4% NOCTURSHAPE™ *blue ingredient*).
- **increased skin firmness** by **14.4%** (applied at 2%) and **23.0%** (applied at 4%) after 30 days.
- provided an **overall reduction of the signs of cellulite**, improving the aspect of cellulite by **12.5%** and **18.4%** (2% and 4% NOCTURSHAPE™ *blue ingredient* respectively)

Cosmetic applications

NOCTURSHAPE™ ***blue ingredient*** can be incorporated into any formulation developed to offer a definition of the silhouette and a smoothening of the skin relief.

The ingredient is designed to provide the formulations with global anti-cellulite, slimming and firming benefits, being especially active during the night hours but also to working during the day.

Technical data

INCI NAME OF THE ACTIVE INGREDIENT

Active ingredient	INCI name
NOCTURSHAPE™ *blue ingredient*	Saccharide Isomerate

PRESENTATION AND PRESERVATIVE

Opaque gel containing 0.5% Saccharide Isomerate.

Code	Product presentation	Preservative
BI080	NOCTURSHAPE™ *blue ingredient*	-

Application data

PROCESSING

NOCTURSHAPE™ *blue ingredient* can be formulated in the aqueous phase of emulsions, creams, gels and lotions in the final step of the manufacturing process. In case of preparing an emulsion, it should be added once the emulsion is formed. In both cases, it should always be provided that the temperature is below 40 °C.

Recommended pH range between 5.5 and 7.5 for NOCTURSHAPE™ *blue ingredient*.

INCOMPATIBILITIES

Strong electrophiles.

SOLUBILITY

Soluble in water.

DOSAGE

A dosage between 2% and 4% of NOCTURSHAPE™ *blue ingredient* is recommended in final cosmetic formulations.

References

1. Ramsey KM, Marcheva B, Kohsaka A, *et al*. The clockwork of metabolism. *Annu. Rev. Nutr*. 27:219-40, 2007.

2. Albrecht U. Timing to perfection: The biology of central and peripheral circadian clocks. *Neuron*. 74(2):246-60, 2012.

3. Eisenstein M. Stepping out of time. *Nature*. 497: 10–12, 2013.

4. Okamura H. Clock genes in cell clocks: roles, actions and mysteries. *J Biol Rhythms*. 19:388-399, 2011.

5. Shostak A, Husse J, Oster H. Circadian regulation of adipose function. *Adipocyte*. 2(4):201-206, 2013.

6. Mehling A, Fluhr JW. Chronobiology: biological clocks and rhythms of the skin. *Skin Pharmacol Physiol*. 19:182-189, 2006.

7. Soudant E. Chronobiology applied to the skin. Expression Cosmetique. November, 2011.

8. Gimble JM, Sutton GM, Ptitsyn AA, et al. Circadian rhythms in adipose tissue: an update. *Curr Opin Clin Nutr Metab Care*. 14:554-561.

9. Johnston JD, Frost G, Otway DT. Adipose tissue, adipocytes and the circadian timing system. Pennington Scientific Symposium: Circadian Biology and Sleep: Missing Links in Obesity and Metabolism?

10. Møller N, Gjedsted J, Gormsen L, et al. Effects of growth hormone on lipid metabolism in humans. *Growth Horm IGF Res*.13 Suppl A:18-21, 2003.

11. Rawlings AV. Cellulite and its treatment. *International Journal of Cosmetic Science*. 28:175–190, 2006.

12. Storsberg J, Stickelmeier L. Cellulite - A (Well-) Known Cosmetic Challenge. SOFW Journal. 137: 2-8, 2011.

13. Kawai M, Rosen CJ. PPARγ: a circadian transcription factor in adipogenesis and osteogenesis. *Nat Rev Endocrinol*. 6:629–636, 2010.

14. Imbeault P, Vidal H, Tremblay A. et al. Age-Related Differences in Messenger Ribonucleic Acid Expression of Key Proteins Involved in Adipose Cell Differentiation and Metabolism. JCE & M. 86(2) 828-833, 2001.

Note: Graphs and photographs of efficacy tests 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.

The specific situation of the trademark in each country may vary and we recommend that you contact us for updated information.

Disclaimer:
While the claims and supporting data provided in this publication are believed to be reliable and they are presented free and for guidance only, there are no warranties of any kind made as to its accuracy, suitability for particular applications, how the product(s) will perform in combination with other substance or in the user's process or the results obtained. All expressed and implied warranties are disclaimed. Lipotec MAKES NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. The recipient is solely responsible for ensuring that products marketed to consumers comply with all relevant laws and regulations and assumes all risk and liability of any use or handling of any materials. Recipient of this publication agrees to indemnify and hold harmless each entity of the Lipotec organization for any and all actions arising from recipient's use of any claims or information in this publication, including, but not limited to, use in advertising and finished product label claims, and not present this publication as evidence of finished product claim substantiation to any regulatory authority. Nothing contained herein is to be considered as permission, recommendation, nor as an inducement to practice any patented invention without permission of the patent owner.