



TIME-FILLER INTENSIVE 5XP

SCIENTIFIC RELEASE

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Sérum correction tous types de rides

Correcting serum -

LABORATOIRES FILORGA HAVE DEVELOPED TIME-FILLER INTENSIVE 5XP, A SERUM INSPIRED BY AESTHETIC MEDICINE TECHNIQUES TO CORRECT ALL TYPES OF WRINKLES: EXPRESSION, DEEP, SURFACE, DEHYDRATION, NECK.



Skin ageing is characterised by a structural deformation of all the layers of the skin. This deformation leads to the appearance of wrinkles, which can be seen as fractures or folds in the skin.

In the epidermis, skin regeneration diminishes as cell renewal slows down.

The epidermis becomes thinner while the thickness of the horny layer increases. The dermal-epidermal junction flattens, reducing exchanges between the epidermis and the dermis. Microcirculation slows down, blood vessels become more fragile and capillary coves, the points of contact where nutrients are supplied, diminish. Cells are no longer as well oxygenated. As a result, cell metabolism decreases and keratinocyte renewal slows down. The epidermis becomes thinner and microcracks appear on the skin's surface.

In the dermis, **fibroblast activity decreases**, leading to a drop in the synthesis of dermal macromolecules such as hyaluronic acid, collagen and elastin, resulting in disorganisation of the extra-cellular matrix. **The dermal network becomes disorganised**.

PHYSIOLOGY OF WRINKLES

The dermis sags and no longer plays its role as the skin's support mattress.

In the hypodermis, **adipocytes atrophy, leading to** fat involution.

ALL THESE STRUCTURAL CHANGES IN THE DIFFERENT LAYERS OF THE SKIN INEVITABLY LEAD TO THE APPEARANCE OF WRINKLES.

When an **aesthetic doctor** observes a patient's face, he or she will distinguish between **different types of wrinkle**, for which he or she will choose **the most appropriate technique**.

Firstly, **expression lines**, which are the result of repeated movements of the facial muscles. Examples include horizontal forehead wrinkles, frown lines and crow's feet. To prevent the appearance of these expression lines, the muscles must be prevented from contracting. To do this, the aesthetic doctor injects the muscles with botulinum toxin, a toxin secreted by the bacterium *Clostridium botulinum.* This substance inhibits acetylcholine, the neurotransmitter responsible for the muscle contraction signal. As a result, the muscles remain relaxed and the skin remains smooth.

Deep wrinkles such as the nasolabial fold are also observed. Over time, the face hollows out, losing bone, muscle and fat. As a result, the skin is no longer held in place, and folds are created under the action of gravity. To plump up deep wrinkles, the aesthetic doctor uses hyaluronic acid filling injections.

The skin may also be dotted with **surface wrinkles**, making the skin texture uneven. These surface wrinkles can be eliminated using the peel technique, which stimulates cell renewal under the action of a keratolytic solution, mainly made up of acids.

The skin can show **dehydration wrinkles**, mainly due to a reduction in water retention in the layers of the skin. The revitalisation injection technique involves injecting a solution of vitamins, minerals and amino acids to stimulate cell metabolism. The cells function better, and the skin's natural hydration mechanisms are maintained.

Finally, there is the **neck wrinkle**, which forms horizontally as a result of repeated head movements. This specific wrinkle, which appears in a particularly fine area, is treated using the tensor thread technique. The principle involves inserting mesh threads under the skin to create a mechanical tensor effect. This tightens the skin without adding volume. These bioresorbable threads also stimulate collagen synthesis^[11].



LABORATOIRES FILORGA PARIS

TIME-FILLER INTENSIVE 5XP

Sérum correction tous types de rides

Correcting serum all types of wrinkles

ACTIVE INGREDIENTS

TIME-FILLER INTENSIVE 5XP serum contains a combination of active ingredients to target all types of wrinkles: a skin-relaxing peptide, plumping peptides, low molecular weight hyaluronic acid, resurfacing sea fennel extract, NCEF, moisturising *Imperata cylindrica* extract, restructuring kangaroo flower extract and tensing polysaccharides.

It should be noted that all the active ingredients have been incorporated at the concentration for which clinical efficacy has been demonstrated. The texture of **TIME-FILLER INTENSIVE 5XP** serum is fluid and light. The product has FILORGA's unique olfactory signature, which combines bergamot, rose and green tea. The formula is made up of 80.11% ingredients of natural origin [calculated according to ISO 16128].

1/ RELAXING PEPTIDE [EXPRESSION LINES]

To correct expression lines caused by repeated muscle movements, **TIME-FILLER INTENSIVE 5XP** incorporates a relaxing peptide, diaminobutyroyl benzylamide diacetate [*Figure 1*]. This is a mediumsized molecule with a molecular weight of 500 Daltons.

This peptide mimics the effect of botulinum toxin, the substance used in injections by aesthetic doctors to block muscle contraction. This active ingredient is



obtained synthetically, and its manufacturing process complies with the 12 principles of green chemistry, which aims to reduce substances that are harmful to the environment [avoiding the production of waste, avoiding wastage, not using/producing compounds that are toxic to humans and the environment, using solvents that cause little pollution, saving energy, using renewable raw materials, etc.]¹²¹.

The peptide used has an inhibitory effect on muscle contraction. The muscle contraction signal is based on communication between a neuron and a muscle cell, at the neuromuscular synapse. The neurons release neurotransmitters, which are chemical messengers sent to the muscle cells. Depending on the nature of the neurotransmitter, the muscle is instructed to contract or remain relaxed. One of the neurotransmitters found at the neuromuscular synapse is acetylcholine. Acetylcholine has an excitatory effect at the neuromuscular synapse. Once released by the neuron, it is recognised by the nicotinic acetylcholine receptors located on the muscle cell membrane, which then receive the contraction message. Nicotinic acetylcholine receptors are cation channels that are activated very rapidly, in a few milliseconds. Activation of these receptors by acetylcholine causes sodium Na+ to enter the cell, producing a depolarisation that leads to skeletal muscle contraction^[3].

The peptide incorporated in **TIME-FILLER INTENSIVE 5XP** is a reversible antagonist of the nicotinic acetylcholine receptor. It blocks the receptor by binding to it and preventing acetylcholine from transmitting its signal. Sodium entry is blocked, the muscle does not receive the contraction signal and therefore remains relaxed [*Figure 2*].

The efficacy of the 4% concentrated peptide was measured in a clinical study on 15 healthy volunteers during 28 days of twice-daily application, by fringe projection with Primos 3D®. Image analysis showed an overall smoothing effect and a reduction in the depth of forehead and crow's feet wrinkles after 28 days of twice-daily application [*Figure 3*].



Figure 2. Diagram of the mechanism of muscle contraction at the neuromuscular synapse and the inhibitory effect of the relaxation peptide on contraction. Source: Technical file Syn-ake - DSM.



Figure 3. In vivo study of the depth of crow's feet wrinkles before and after 28 days of twice-daily application of a formula containing 4% of the peptide. Source: Technical file Syn-ake - DSM.

2/ PLUMPING PEPTIDES [DEEP WRINKLES]

To target deep wrinkles, **TIME-FILLER INTENSIVE** 5XP contains a synergistic combination of two peptides: palmitoyl tripeptide-1 and palmitoyl tetrapeptide-7.

The synthesis of these peptides complies with 8 out of 12 green chemistry principles. These two peptides have been coupled with palmitic acid to optimise their penetration into the skin.

These peptides are the result of advances in our understanding of skin repair mechanisms. The healing process involves peptide fragments derived from the breakdown of matrix proteins in the dermis, such as collagen, elastin and fibronectin. These fragments are messengers capable of regulating the activity of fibroblasts in order to regenerate tissue^[4].

The peptides used in **TIME-FILLER INTENSIVE 5XP** serum have the following amino acid sequences: GHK and GQPR. These sequences are similar to those of the peptides found in the dermis during wound healing. They act by bio-mimetic means, stimulating the synthesis of collagen I, fibronectin and hyaluronic acid, while guaranteeing good tolerance.

THE EFFICACY OF THE 2 PEPTIDES WAS ASSESSED IN AN IN VITRO STUDY ON THE NEOSYNTHESIS OF COLLAGEN I, FIBRONECTIN AND HYALURONIC ACID **BY HUMAN FIBROBLASTS [FIGURE 4].** A SYNERGISTIC EFFECT BETWEEN THE 2 PEPTIDES WAS OBSERVED COMPARED **TO PEPTIDES ALONE** [Figure 4].

A synergistic effect between the 2 peptides was observed compared to peptides alone:

/ Collagen I : +258% / Fibronectin : + 164% / Hyaluronic acid : + 179%

THE EFFECTIVENESS OF THE PEPTIDE COMPLEX ON WRINKLES WAS ASSESSED IN AN IN VIVO STUDY. STUDY PROTOCOL:

- / 24 female volunteers aged between 35 and 45
- / Application of a cream containing 3% of a peptide solution to one half of the face and application of a placebo cream to the other half of the face
- / Applied morning and evening for 2 months



Evaluation by profilometry demonstrated a significant reduction in wrinkle depth of -19.9% and wrinkle volume of -23.3% compared to placebo. Excellent anti-wrinkle efficacy can be observed after 2 months of twice-daily use [Figure 5].



Figure 4. In vitro study on the neosynthesis of matrix fibres by human fibroblasts fibroblasts in the presence of GHK and GQPR peptides alone and in combination

3/ LOW MOLECULAR WEIGHT HYALURONIC ACID [DEEP WRINKLES]

Low molecular weight hyaluronic acid¹ is a hyaluronic acid with a short chain. Because of its small size, it can easily penetrate the deep layers of the skin, right down to the dermis. It retains water in the skin and therefore has a moisturising effect^[5]. The hyaluronic acid in **TIME-FILLER INTENSIVE 5XP** has a molecular weight of 3-10 kDa.

Low molecular weight hyaluronic acid also has regenerative properties. It has the ability to The hyaluronic acid used by Laboratoires FILORGA stimulate cell proliferation and boost endogenous is of natural origin, obtained by biofermentation.

acid is considered high molecular weight when its molecular weight is greater than or equal to 1000 kDa.



Figure 5. Visible reduction in crow's feet wrinkles after 2 months of twice-daily use of a cream containing the peptide complex.

production of hyaluronic acid and collagen I. The half-life of hyaluronic acid in the skin is 24 hours. It must therefore be constantly renewed. When hyaluronic acid is broken down in the skin, the hyaluronic acid fragments indicate to the cells that they need to reproduce it. Low molecular weight hyaluronic acid mimics this mechanism and boosts hyaluronic acid production.



Similarly, sea fennel stimulates the expression of the CRABP II receptor, which increases cell multiplication and therefore thickens the epidermis.

Sea fennel also acts on the adhesion of corneocytes. It reduces the expression of genes coding for desmocollins 3 and 4 and desmoplakins I, II and III, proteins that make up corneodesmosomes and ensure the cohesion of corneocytes.

A reduction in these proteins leads to more rapid desquamation, resulting in a reduction in the thickness of the stratum corneum.

The *in vitro* study demonstrated that 1% sea fennel extract increased the thickness of the epidermis while visibly reducing the thickness of the horny layer [Figure 7].

4/ RESURFACING SEA FENNEL EXTRACT [SURFACE WRINKLES]

INTENSIVE 5XP contains an extract of sea fennel [Crithmum maritimum]. Sea fennel is a plant belonging to the Apiaceae family, found by the sea, France. exposed to the wind, on cliff edges and on rocks [Figure 6]. Sea fennel is found on the Channel, Atlantic and Mediterranean coasts. It is also found in coastal areas from Iceland to the Canary Islands, on the shores of the Black Sea and along the coast of Western Asia.

Introduced into the French Pharmacopoeia in 1837, it has been known since Antiquity. Sailors took it with them on their voyages because of its high vitamin C and mineral content.

To smooth surface wrinkles, **TIME-FILLER** The extract used is obtained by supercritical CO₂ extraction of sea fennel wax. The sea fennel used in TIME-FILLER INTENSIVE 5XP comes from Brittany.

> Sea fennel has a similar action to retinoids in its ability to stimulate epidermal renewal. Its mechanism of action has been studied by in vitro tests on reconstructed epidermis.

> Retinoids stimulate keratinocyte multiplication via the binding of the intracellular receptor CRABP II [Cellular Retinoic Acid Binding Protein], and reactivate the synthesis of CRABP receptors^[6].

The pro-inflammatory activity of 1% samphire was studied in comparison with retinoids. Unlike retinoids, sea fennel does not induce the expression of genes coding for interleukin 1-alpha, a mediator of inflammation, confirming good skin tolerance.

An in vivo study was carried out to assess the efficacy of 1% sea fennel extract after 28 days of twice-daily application.

The study examined skin isotropy, a parameter that defines the orientation of skin micro-furrows. After 28 days of application, an increase in the isotropy factor was observed, reflecting a multi-directional orientation of the micro-furrows and therefore a smoothing effect [Figure 8].



Figure 7. In vitro study of the efficacy of 1% marine fennel in increasing epidermal thickness and reducing the thickness of the horny layer.



Figure 8. Microscopic observation of skin micro-relief before and after 28 days of twice-daily application of _____ sea fennel extract.

5/ MOISTURISING IMPERATA CYLINDRICA EXTRACT COMBINED WITH NCEF [DEHYDRATION WRINKLES]

To fight dehydration wrinkles, TIME-FILLER INTENSIVE 5XP contains an extract of Imperata cylindrica root combined with NCEF [New Cellular Encapsulated Factors], the unique core formula from Laboratoires FILORGA.



5.1. Imperata cylindrica extract

Imperata cylindrica is a herbaceous plant in the Poaceae family, native to South-East Asia [Figure 9]. This plant has the ability to adapt to extreme climatic conditions such as drought and salinity. Its roots are particularly rich in mineral salts, especially potassium.

Potassium plays an essential role in maintaining the body's water homeostasis. In eukaryotic cells, there is a difference in the concentration of mineral ions between the intracellular and extracellular environments, creating an ionic gradient. Cells favour an intracellular over-concentration of potassium K+ and a deficit of sodium Na+.

These differences in concentration are maintained by a Na+/K+ pump that actively pumps K+ into the cells and expels Na+. The ionic gradient thus created contributes to a continuous osmotic influx of water into the cell. To function correctly, this pump must be activated by an influx of extracellular potassium into the cell^[7].

AS THE ROOTS OF IMPERATA CYLINDRICA ARE PARTICULARLY RICH IN POTASSIUM. THEY ACT AS PUMPS THAT CAPTURE WATER, **ENABLING THE PLANT TO SURVIVE PERIODS** OF DROUGHT. THANKS TO ITS INCREDIBLE HYDRATING PROPERTIES, IMPERATA **CYLINDRICA CREATES A RESERVOIR** OF WATER IN THE SKIN.



An in vivo study involving 12 volunteers assessed the moisturising properties of a gel containing 3% Imperata cylindrica extract after 2 applications at 0 and 7 hours.

Measurement of the hydration rate by corneometry 24 hours after application showed a significant increase of +20% compared with the control and with TO.

Keratinocyte turgidity was observed after application of Imperata cylindrica, which also indicates cellular hydration [Figure 10].



Figure 10. Keratinocytes 24 hours after application of placebo [left] and Imperata cylindrica extract [right] observed by scanning electron microscopy.



5.2. NCEF

NCEF is the unique core formula of Laboratoires FILORGA. It contains high molecular weight hyaluronic acid and revitalising ingredients used in injections [amino acids, vitamins, minerals, co-enzymes]. NCEF provides elements that are essential for cells to function properly, while respecting the skin's natural mechanisms. In order to pass through the skin barrier, the ingredients are encapsulated in multi-lamellar liposomes.

NCEF acts like a real booster, activating the skin's natural cellular mechanisms to combat the signs of ageing.

To verify the efficacy of NCEF, FILORGA carried out *ex vivo* tests on human skin explants. The results showed a stimulation of fibroblast activity with a significant increase of 70% in collagen I and 22% in elastin compared to the control [*Figure 11*].



Figure 11. Skin explants observed by fluorescence microscopy. Measurement of the amount of collagen before [top left] and after application of NCEF [top right]. Measurement of the amount of elastin before [bottom left] and after application of NCEF [bottom right]. Green: collagen, elastin; blue: cell nuclei.





6/ RESTRUCTURING KANGAROO FLOWER EXTRACT [NECK WRINKLES]

To correct neck wrinkles, **TIME-FILLER INTENSIVE 5XP** contains certified organic kangaroo paw [Anigozanthos flavidus] flower extract from Australia [Figure 12]. Kangaroo paw, so called because of the shape of its inflorescence, is a plant endemic to south-western Australia, belonging to the Haemodoraceae family.

Due to its high nectar content, kangaroo paw contains a large amount of natural sugar. The flower also contains flavonoids with antioxidant and anti-inflammatory properties.

The kangaroo paw targets a new marker of dermal architecture, tenascin X. Tenascin X is a glycoprotein in the extra-cellular matrix of the dermis which plays a crucial role in regulating the spacing between collagen fibrils and elastin fibres^[8]. After 28 days of twice-daily use, there was a significant 30% reduction in the appearance of neck wrinkles compared with placebo [*Figure 14*].

Kangaroo paw increases the synthesis of tenascin X, which helps to restructure dermal tissue. An *in vitro* study was conducted on human dermal fibroblasts in the presence of 0.1 and 0.2% kangaroo paw extract. A significant +39% increase in tenascin X was observed compared to the control [*Figure 13*].



7/ TENSOR POLYSACCHARIDES

TIME-FILLER INTENSIVE 5XP is formulated with a natural tensing biopolymer made from the carrageenans of red seaweed [Kappaphycus alvarezii] and tara gum [Caesalpinia spinosa]. This biopolymer forms a protective film on the skin's surface. It smoothes the skin's microrelief to instantly reduce wrinkles.

EFFECTIVENESS ON NECK WRINKLES WAS ASSESSED *IN VIVO* USING 3D ANALYSIS. STUDY PROTOCOL:

- / 39 volunteers aged between 45 and 65
- / Application of a cream containing 2% kangaroo paw extract
- / Application morning and evening for 28 days



Figure 14. Image analysis of neck wrinkles before and after 28 days of twice-daily application of kangaroo paw extract.

EFFECTIVENESS TESTS

1/ RESULTS OF EX VIVO STUDY

FILORGA conducted an ex vivo study on human skin explants to investigate the effects of TIME-FILLER **INTENSIVE 5XP** serum on collagen expression. Collagen is a protein essential for skin firmness. There are 28 different types of collagen in the human body. In the skin, type I collagen is the most common, but types III, IV, V and VII are also present. FILORGA has studied the effects of TIME-FILLER INTENSIVE **5XP** serum on collagens I, IV and VII:

- / Collagen I : the most abundant, representing around 90% of dermal collagen. It forms fibers that help maintain skin firmness.
- / Collagen IV : present at the dermal-epidermal junction. It is involved in the formation of the dermal-epidermal junction network, which is crucial to skin structure.
- / Collagen VII : serves as an anchoring collagen to link the various elements of the dermal-epidermal junction.

Collagen I was studied by immunofluorescence and collagens IV and VII by immunohistochemistry. The anti-aging effect was analyzed using a UV model. 3 conditions were compared per donor [n=6 donors]:

- / Untreated skin
- / UV-exposed skin
- / UV-exposed skin + TIME-FILLER **INTENSIVE 5XP** serum

These skin fragments were kept alive for 12 days for analysis of type I collagen in the dermis, and for 5 days for analysis of collagens IV and VII at dermal-epidermal level. TIME-FILLER INTENSIVE 5XP was applied once a day to the skin surface, after UV exposure.

The study demonstrated a significant increase in collagen after UV exposure and application of TIME-FILLER **INTENSIVE 5XP**, compared to UV-exposed skin without product [Figure 15] :

- / +60,4% collagen I [p<0,05]
- / +78,9% collagen IV [p<0,05]
- / +34% collagen VII [p<0,05]











Figure 15. TIME-FILLER INTENSIVE 5XP serum induces a significant increase in collagen types I, IV and VII after UV exposure, compared to UV-exposed skin without product application. From top to bottom: collagen I, collagen IV, collagen VII. Ex vivo study on human skin explants. Collagen I marked green by immunofluorescence. Collagens IV and VII marked in red by AEC [3-amino-9-ethylcarbazole]. *p<0,05.

- type I collagen in the dermis, as well as type IV and VII collagen at the dermal-epidermal junction, after UV treatment.
- / These results demonstrate the anti-aging efficacy of TIME-FILLER INTENSIVE 5XP serum on the skin's main collagens.

/ TIME-FILLER INTENSIVE 5XP serum has a protective effect against photoaging. It significantly increases

2/ RESULTS OF THE CLINICAL STUDY

A dermatologically controlled 28-day clinical study was conducted to assess the efficacy of TIME-FILLER INTENSIVE 5XP serum.

- Description of the volunteer panel:
- / 30 Caucasian women.
- / Aged between 35 and 65
- / Fitzpatrick phototype II to IV
- / Wrinkles on forehead, glabella, crow's feet, nasolabial fold and neck.
- / All skin types [normal, dry, combination, oily] included 57,6% sensitive skin.
- / Apply serum twice a day, morning and evening, to face and neck.

The following skin parameters were assessed on D0, D7 and D28:

- / Clinical scoring: forehead wrinkles, glabella wrinkles, crow's feet, nasolabial folds and horizontal neck wrinkles.
- / AEVA [3D acquisition]: anti-wrinkle efficacy and smoothing effect.
- / Cutometry: viscoelastic properties.

Results showed a significant improvement in all types of wrinkle after using TIME-FILLER INTENSIVE 5XP serum [Table 1, Figures 16 et 17]. An immediate and long-term smoothing effect was also observed, as well as an improvement in skin firmness and elasticity.

Wrinkle	7 days	28 days
Forehead	ns	-14,1%*
Glabella	-4,9%*	-22,5%*
Crow's feet	-2,3%*	-13,6%*
Nasolabial fold	ns	-5,1%*
Neck	-4,1%*	-21,1%*

Table 1. Clinical scoring of wrinkles after twice-daily use of ${\it TIME-FILLER}$ INTENSIVE 5XP serum. Average % relative difference compared with D0. ns: not significant. *p<0.05 compared with D0.



DO













Figure 16. 3D illustration of different wrinkle types after twice-daily use of **TIME-FILLER** INTENSIVE 5XP serum. From top to bottom: forehead wrinkles in subject n°29, glabella wrinkles _ in subject n°27, crow's feet wrinkles in subject n°11, nasolabial fold in subject n°18, neck wrinkles in subject n°30.





Figure 17. Standardized photographs of wrinkle types after 28 days of twice-daily use of TIME-FILLER INTENSIVE 5XP serum. From top to bottom: forehead wrinkles, glabellar lines, crow's feet, nasolabial fold.

3/ SELF-EVALUATION QUESTIONNAIRE

A self-assessment questionnaire was also completed by each study volunteer. It was used to measure the appreciation of each volunteer after using the product.

The product's organoleptic properties were highly appreciated, with 100% of women declaring that from the very first application they were satisfied with the texture, penetration and sensation of comfort.

QUESTIONNAIRE RESULTS

- effect and that the skin looked smoother. 94% of women declared that the product had an immediate smoothing action.
- / After 7 days' use, 91% of women said the product had a tightening effect and 94% said it seemed to relax the features.
- /After 28 days of use, 97% of women said their skin looked smoother, and 82% observed that their wrinkles were less deepened.



TOLERANCE TESTS

Dermatological tolerance was tested in conjunction with efficacy, using the same application methods. The dermatologist in charge of the study assessed the product's tolerance after 28 days of twice-daily use.

SKIN COMPATIBILITY AND ACCEPTABILITY, WITH NO REACTIONS OR FEELINGS OF DISCOMFORT OVER THE DURATION OF THE STUDY.

/ From the very first application, 97% of women declared that the product had an immediate smoothing

THE EVALUATION DEMONSTRATED VERY GOOD



TIME-FILLER INTENSIVE 5XP

Sérum correction tous types de rides Correcting serum all types of wrinkles

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NOTES



1^{st*} FRENCH AESTHETIC MEDECINE LABORATORY

Laboratoires FILORGA originally designed, developed and manufactured injectables used by leading aesthetic doctors, dermatologists and plastic surgeons throughout the world. In order to make their expertise in aesthetic medicine accessible to everyone, Laboratoires FILORGA created a range of anti-ageing skincare formulated with NCEF [New Cellular Encapsulated Factors], a unique polyrevitalising complex encapsulating active ingredients used in injectables. The advanced formula led to the development of creams that offered real anti-ageing performance, with visible results after 7 days^[9].



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