



PLURIAL BIOFILLERS

THE FIRST BIOSTIMULATING FILLERS



Pluryal
injectables

**YOUR MOST
BEAUTIFUL
AGE IS NOW!**

MD SKIN SOLUTIONS LABORATORIES

AT A GLANCE

2ND GENERATION FAMILY BUSINESS

13

YEARS

15M

TREATMENTS

70

COUNTRIES

PLURIAL INJECTABLES

REVIVING SELF-CONFIDENCE

THE WIDEST RANGE OF INJECTABLES ON THE MARKET

08

FILLERS

04

DENSIFIERS

02

INTIMATES

04

TECHNOLOGIES



OUR SCIENCE IS EXCELLENCE

Pluryal is actively focused on promoting individual and natural standards of beauty that improve one's look whilst preserving their identity as it firmly believes that every person should feel self-confident and beautiful at any age.

Pluryal is committed to innovation and dedicates a significant percentage of its yearly revenues to R&D in order to develop cutting-edge solutions that promote the "Pro-Aging" revolution and provide patients around the world with comprehensive treatments that not only improve the skin, but also the hair and body.

Keeping in line with its "Pro-Aging" philosophy, Pluryal releases an innovative concept of densifiers, a brand-new generation of injectable devices designed to treat the skin (face and body), the hair and intimate areas.



CATEGORIES OF PLURYAL® INJECTABLES

FILLERS, DENSIFIERS & INTIMATES
(ESSENTIALS/PN/BIO/LIDOCAINE)

FILLERS

Essentials:

Booster
Classic
Volume

Bio:

Bioclassic
Biovolume

Lidocaine:

Classic Lidocaine
Volume Lidocaine
Contour Lidocaine

DENSIFIERS

PN:

Silk
Densify
Hair Density

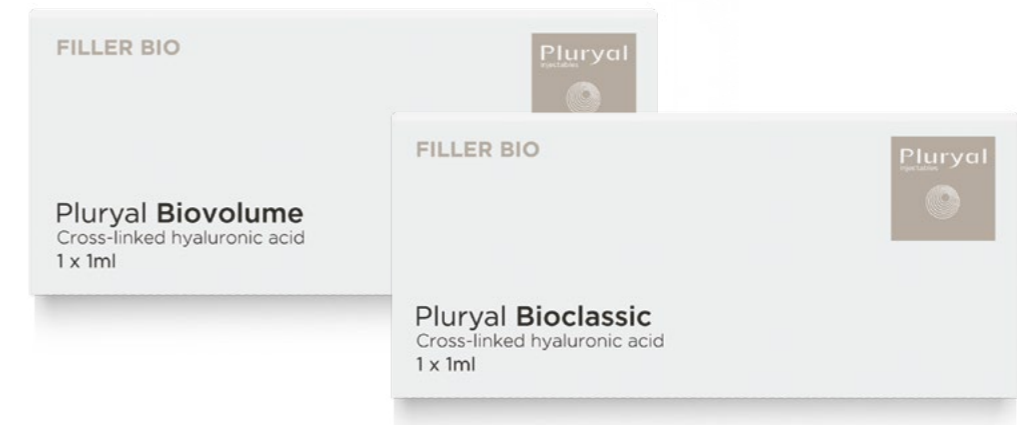
Bio:

Biosculpture

INTIMATES

Bio:

Biointimate
Biointimate Volume



PLURIAL® BIOFILLERS

THE FIRST BIOSTIMULATING FILLERS

WHY A “BIOFILLERS” RANGE?

The market of minimally invasive procedures is rapidly growing due to the rise in aesthetic consciousness and the increase in the proportion of the world’s older population. The nature of patients’ demand is also changing. With the increased transparency, spread of knowledge and under the influence of social media, patients are more and more requesting preventive and safe treatments. Besides, a particular attention is paid to “clean beauty” products that respect and preserve the environment. This is manifested in a growing number of younger patients who are looking for soft and bio-respectful products.

FROM “FILLERS” TO “BIOFILLERS”

Fillers are used to restore the lost volumes in the face and lips.

Biofillers are a new generation of fillers. They do not just act as fillers, they also improve the skin’s quality by boosting hydration levels deep within the skin, increasing its smoothness, elasticity and firmness.

In addition, they are produced according to a manufacturing process which allows having the lowest possible level of residual BDDE (1,4-Butanediol Diglycidyl Ether) in the finished product for an increased safety and biocompatibility.



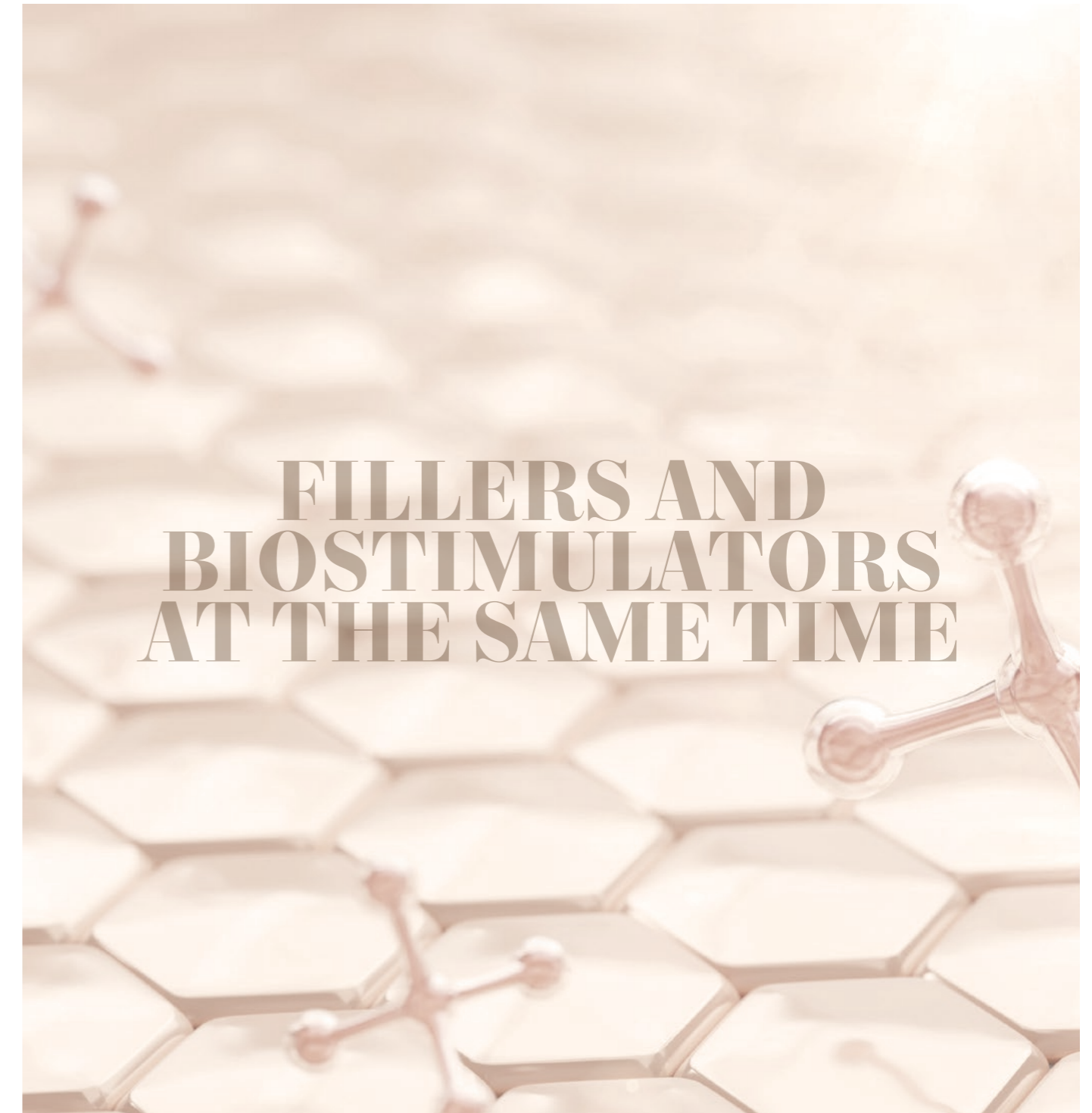
PLURIAL® BIOFILLERS

THE FIRST BIOSTIMULATING FILLERS

The Pluryal® Biofillers are different from regular dermal fillers in several aspects:

In their action

Regular fillers are used to restore the volumes of the skin, by filling the depressions. Pluryal® BIOCLASSIC and Pluryal® BIOVOLUME, on the other hand, act beyond regular fillers as they also increase the skin’s quality by boosting the hyaluronic acid and elastin levels deep within the skin which tend to decrease with age, causing a tired skin appearance. By doing so, the Pluryal® Biofillers not only **restore the lost volumes**, but they also **improve the quality of the skin**, increasing its smoothness, elasticity and firmness.



In their safety

Regular hyaluronic acid fillers use a cross-linking agent (a chemical) to increase the durability of the hyaluronic acid and prevent the hyaluronidase enzyme as well as hydroxyl radicals from eliminating the product, because our own body has the capacity of rapidly degrading hyaluronic acid.

Thanks to a very unique manufacturing process called MATRICYAL 3D TECHNOLOGY®, the Pluryal® Biofillers incorporate the lowest percentage possible of cross-linking agent to increase the safety and the biocompatibility of the products on the skin.

In the final product, the residual BDDE (the crosslinking agent used) is 20 times less than the safety level authorized by European and American regulations.



PLURYL® BIOFILLERS

THE FIRST BIOSTIMULATING FILLERS

In their respect to the environment

Pluryal® Biofillers respect the planet and are environmentally friendly. Their production process is in compliance with ISO14001 norms; they use the purest materials, which are free from polluting chemical substances. Moreover, their packaging is totally degradable and strictly abides by FSC's standards.



Respect
the planet



Environmentally
friendly



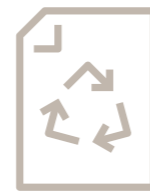
Compliance with
ISO14001 norms



Purest
materials



Free from polluting
chemical substances



Made from
degradable material

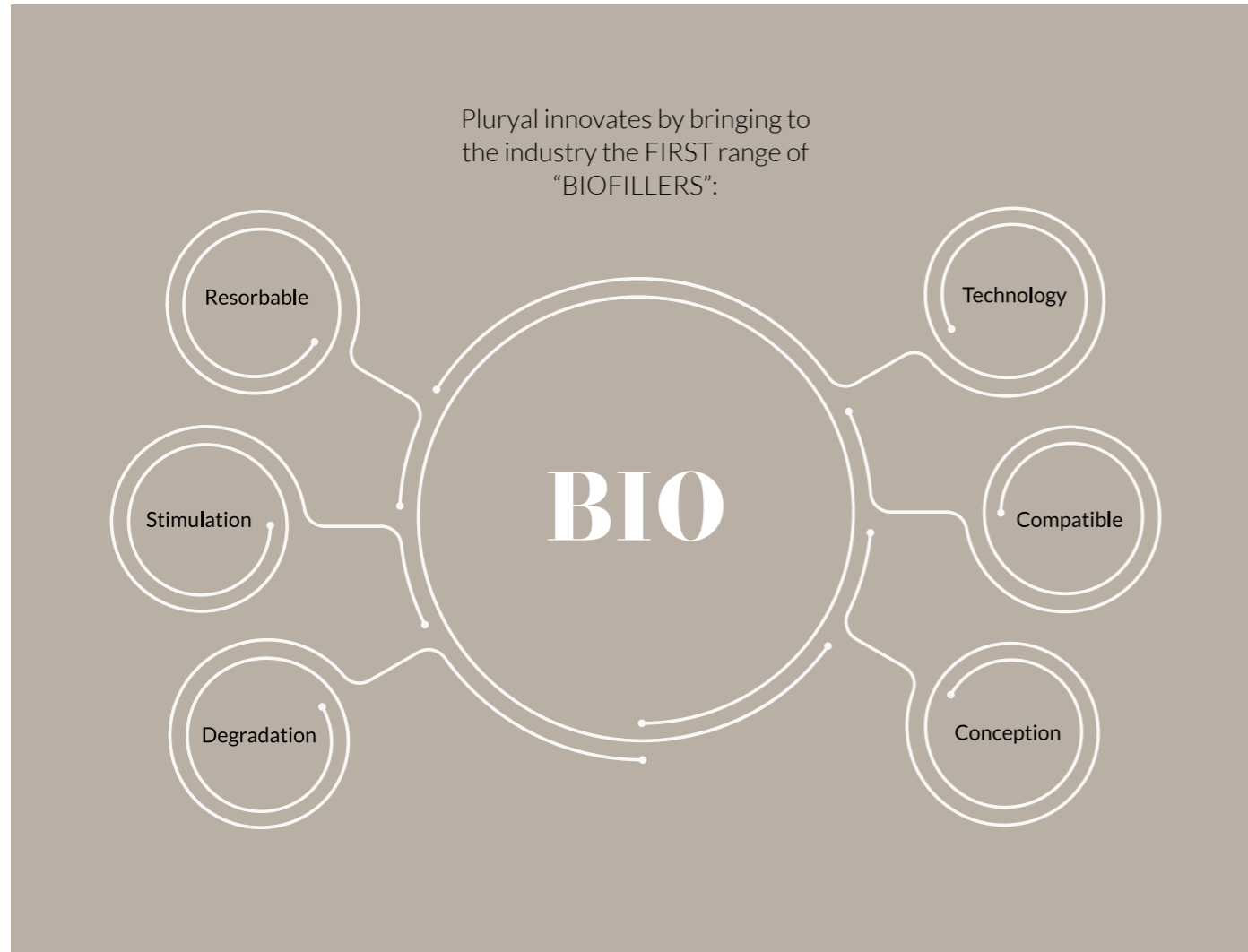
ENVIRONMENTALLY FRIENDLY



PLURIAL[®] BIOFILLERS

THE FIRST BIOSTIMULATING FILLERS

PLURIAL[®] BIOFILLERS: AN INNOVATION



KEY FACTS ABOUT PLURIAL[®] BIOFILLERS:

1 They are manufactured in Europe in compliance with EU regulations and EC certification

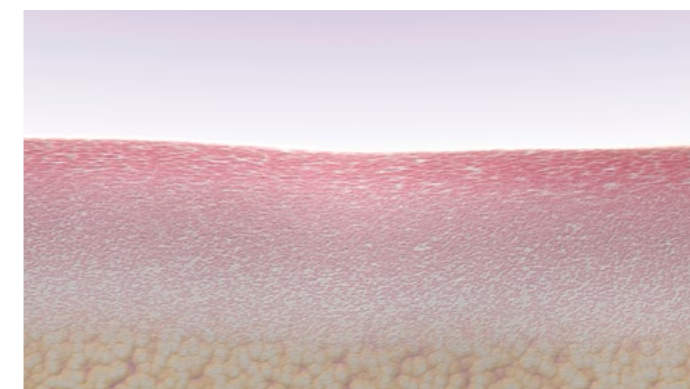
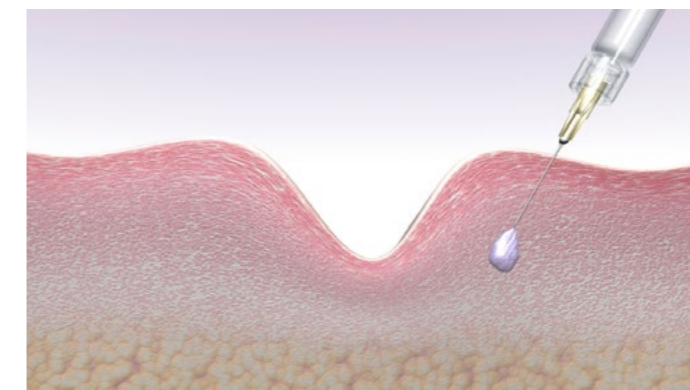
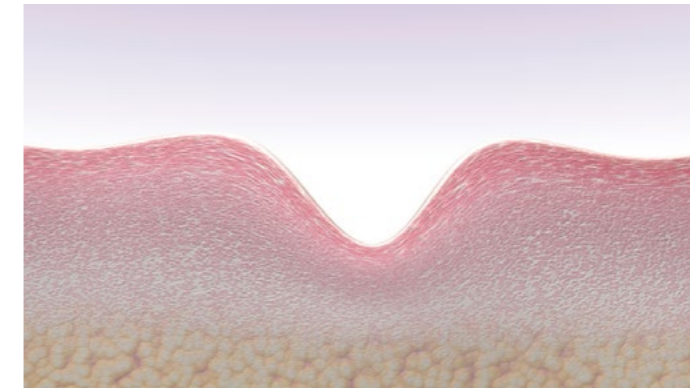
2 They use an innovative, patented and unique technology: MATRICYAL 3D[®]

3 They are a new generation of biostimulating fillers

PLURIAL[®] BIOFILLERS

MINDFUL BIO BEAUTY: WHEN BEAUTY GETS MORE CONSCIOUS

The superior plasticity of the Plural[®] Biofillers ensures a better penetration, greater power and speed of spreading than traditional fillers for an optimal tissue distribution. The effect is hence more natural.



PLURIAL[®] BIOFILLERS, the biostimulating effect

Plural[®] Biofillers, thanks to the free HA they contain, biostimulate the skin by binding with cell receptors, mainly CD44 receptors^[1].

This stimulation of cellular receptors increases the quantity of hyaluronic acid and fibronectin, which has various biological roles in the skin: a growth factor, an adhesion molecule, as well as a chemotactic agent for fibroblasts and it contributes to collagen fibril deposition and assembly. In addition, it controls the migration of keratinocytes in the skin's healing process.

PLURIAL® BIOFILLERS

MINDFUL BIO BEAUTY: WHEN BEAUTY GETS MORE CONSCIOUS

PLURIAL® BIOFILLERS derived from biotechnology

They are based on hyaluronic acid, a glycosaminoglycan naturally found in the skin (50% of the body's hyaluronic acid is in the dermis), which is produced by bio-fermentation of *Streptococcus equi* subspecies zooepidermicus (a strain non-pathogenic for humans) and highly purified.

HA is a substance offering very low immunogenic risks when it is derived from biotechnology (bacterial fermentation of *Streptococcus equi* on a plant-derived substrate). This particularly safe, sterile, transparent, non-pyrogenic, iso-osmotic, and isotonic gel is also bio-resorptive over time.



PLURIAL® BIOFILLERS offer an unprecedented safety

A particular attention was paid to reducing the residual content of BDDE in the finished product. BDDE is the cross-linking agent involved in the "active matrix" technology used to develop the Pluryal® Biofillers range.

During the manufacturing process:

1. Residual BDDE is removed from the product with a dialysis process, ensuring traces of it do not exceed 0.1 ppm, a level which is 20 times lower than the authorized FDA limit of 2 ppm.
2. Almost no nucleic acids or proteins (traces: <0.1%) can be found in the finished product guaranteeing the best quality and absolute safety.

PLURIAL® BIOFILLERS protect the environment

The manufacturing process (ISO 13485) and industrialization bio-process (ISO 14001) comply with the strictest environmental standards. In addition, the packaging of the product is entirely recyclable and environmentally friendly.

MATRICYAL 3D

A UNIQUE BIOPROCESS ALLOWING
THE LOWEST POSSIBLE LEVEL OF BDDE



MATRICYAL 3D TECHNOLOGY®

A BIO INNOVATION

Pluryal® Biofillers are manufactured using an innovative technology called MATRICYAL 3D TECHNOLOGY® which consists in using **3 different types of highly purified hyaluronic acid**, combined in a layered process:

1. The **active matrix** consisting of two types of HA cross-linked with BDDE, concentrated at 25mg/ml: High (2 Million Da) and Medium (1 Million Da) molecular weights HA, to restore the volumes and **act as a filler**
2. The embedded matrix consisting of **free HA** of Medium molecular weight (1 Million Da), protected from enzymatic degradation thanks to the matrix's structure, and which **acts as a biostimulator**.

This innovative technology uses a 3D matrix which allows having **the lowest possible level of residual BDDE (< 0.1ppm)** thanks to a long reticulation time at low temperature.

Controlled-release 3D matrix

FIG.1 : GENTLE CROSS-LINKING OF TWO HYALURONIC ACID WITH TWO DIFFERENT MOLECULAR WEIGHTS

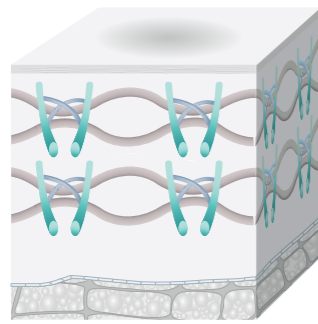
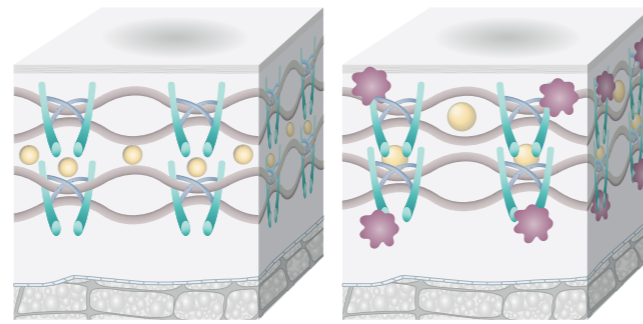


FIG.2 : LAYERING OF NATIVE HYALURONIC ACID



A cross-linked HA layer alternated with one free HA layer

The layered free HA is protected against enzymatic degradation and is released slowly

2 million Dalton HA 1 million Dalton HA BDDE Free HA Enzyme

STEP 1:

SOLID 3D ACTIVE MATRIX CREATION (FIG. 1)

Long crosslinking time at low temperature to get a non-calibrated, single-phase gel with optimum viscosity. 2 types of hyaluronic acid of different molecular weights (2 Million Da and 1 Million Da) are crosslinked with BDDE to form a solid 3D Matrix.

ADVANTAGES:

1. The low mixing speed and the long crosslinking time make the crosslinking agent disperse itself more evenly and reduce the quantity of BDDE used, resulting in a very low residual BDDE level in the finished product (<0.1 ppm).
2. The low temperature limits the depolymerization of the sodium hyaluronate used as a raw material to preserve its rheological properties.

MATRICYAL 3D TECHNOLOGY®

A BIO INNOVATION

STEP 2:

LAYERING OF FREE HA LAYERS INTO THE 3D ACTIVE MATRIX (FIG. 2)

Free hyaluronic acid molecules (1 Million Da) are inserted at the core of the crosslinked hyaluronic acid layers to complete the 3D Matrix, one crosslinked layer alternated with a free hyaluronan layer.

ADVANTAGES:

1. Because the free HA is layered in the network, it is protected from hyaluronidase enzymatic degradation.
2. This free HA is gradually released over time providing a bio-stimulating effect.

RESULTS

1 Double effect: filling and biostimulating

2 Increased safety (residual BDDE <0.1ppm)

3 Better distribution and plasticity: natural results

4 More expanding power in the tissue

MATRICYAL 3D TECHNOLOGY®

A BIO INNOVATION

BENEFITS ON THE SKIN [2,3,4,5]

The MATRICYAL 3D Technology® allows the elaboration of a very unique hyaluronic acid product where the HA particles are much smaller than those used in standard products.

This promotes the penetration and distribution of Pluryal® BIOCLASSIC and Pluryal® BIOVOLUME in the tissues, preventing the occurrence of any “string effect” and promoting more natural-looking results.

INTENSE HYDRATION AND FILLING

High and Medium Molecular Weights HA: 2 Million and 1 Million Da

The High Molecular Weight HA of the active matrix offers **hydration and protection properties by capturing water molecules and free radicals** and boosting metabolic exchanges.

Cross-linked HA with BDDE features a slower degradation than free HA and a longer aesthetic effect. The gel integrates perfectly into the skin and fills it durably.

REJUVENATION/REGENERATION

Free Embedded Medium Molecular Weight HA: 1 Million Da

Free Embedded HA molecules are protected from quick degradation thanks to the 3D matrix. When released, they induce a bio-revitalizing effect. Binding with CD44 cell receptors, they stimulate endothelial cells, **promoting neo-angiogenesis and collagen synthesis.** [6]

It stimulates the skin over time.

RESTRUCTURATION

Regarding High Molecular Weight Cross-Linked HA (matrix):

The bio-degradation is slower: the HA molecules gradually biodegrade and react with CD44 receptors [7], **inducing the release of IL-4, IL-10**, reducing the aseptic inflammation reaction activity and affecting IL-1b and PG-E[8]. This results in suppressing inflammation and free radical activity. [9,10]



THE FIRST
BIOSTIMULATING
FILLERS



BIO-STIMULATION

RESTRUCTURED SKIN, RESPONSIBLE BEAUTY

1. Visible results as of the first session
2. Improved skin quality
3. Perfect for volume increase
4. Spreads perfectly well in tissues
5. Adapts to the face's natural shapes
6. Green product

FILLER BIO

Pluryal Bioclassic
Cross-linked hyaluronic acid
1 x 1ml




Pluryal
injectables
FILLER BIO

Pluryal Biovolume
Cross-linked hyaluronic acid
1 x 1ml



Pluryal
injectables



WHO IS A CANDIDATE FOR PLURYAL® BIOFILLERS?

Pluryal® BIOCLASSIC & Pluryal® BIOVOLUME are designed to treat regular skin areas which need to be rejuvenated:

Everyone can benefit from this treatment, but mainly patients who are:

1. Looking for an efficient treatment for sagging skin, volume loss & flaccidity
2. Wanting to use environmentally friendly products
3. Asking for a moisturizing treatment that restores the natural osmolarity of soft tissues
4. Wishing to stimulate dermal & hypodermal tissue receptors
5. Desiring a flawless skin & natural results

PLURIAL® BIOCLASSIC

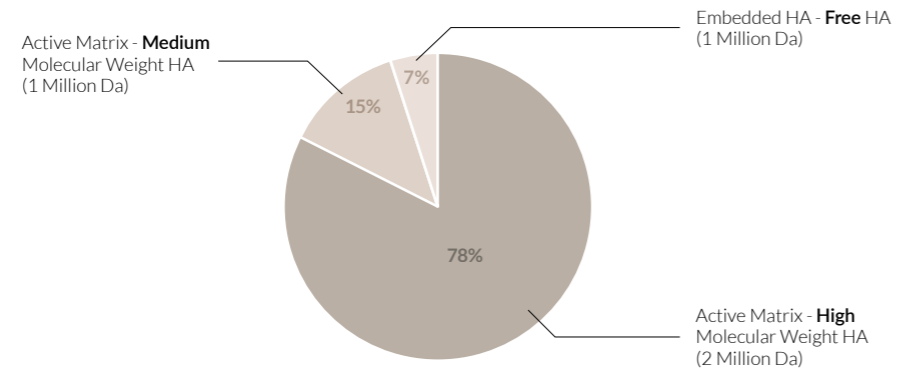
MEDIUM BIOFILLER

Pluryal® BIOCLASSIC is an injectable medical device based on the MATRICIAL 3D TECHNOLOGY®. It is a safe, sterile, transparent, apyrogenic, physiological and bio-resorbable-over-time gel.

It targets the moderate loss of volume, skin sagging and medium wrinkles.

Composition: 25 mg/ml of hyaluronic acid, including 7% free hyaluronic acid embedded in the 3D matrix.

Distribution of the different HA in the matrix of Pluryal® Bioclassic



Other ingredients: Phosphate buffer, NaCl

Cross linking: +++ (BDDE < 0.1 ppm)

Extrusion Force (N): 23

G' factor (mPa): 100,000

Sterilization: Steam

Endotoxins (EU/mL): < 20

Indications

Treatment of imperfections that require an enrichment of the facial tissue with volumetric increase.

1. Moderate loss of volume and wrinkles
2. Skin sagging
3. Skin quality

Volumetric action

The product physiologically restores the volumes

Re-structuring action

Improvement of tissues through cell receptor stimulation

Moisturizing action

Re-integrates the natural osmolarity of tissues

Level of Injection: Mid to deep dermis

Maintenance treatment: Every 5-8 months or as required

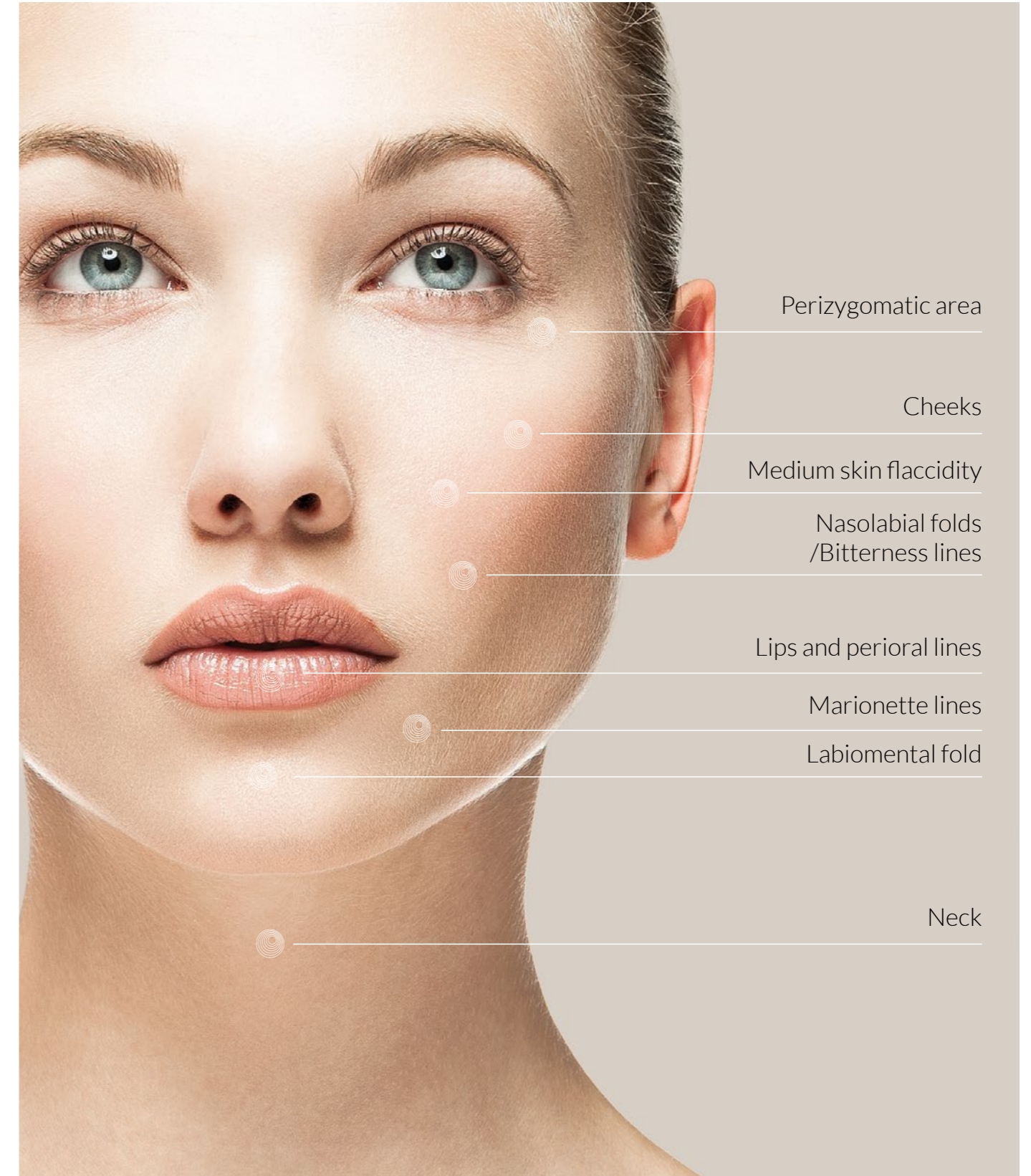
Pack Contents: 1 x 1 ml pre-filled syringes | 27G x 13 mm needle | 27G x 19 mm needle

Regulatory: Syringe (CE 0373, MD Skin Solutions) | Needles (CE 0123, Sterimedix)

PLURIAL® BIOCLASSIC

MEDIUM BIOFILLER

TARGET AREAS



Perizygomatic area

Cheeks

Medium skin flaccidity

Nasolabial folds
/Bitterness lines

Lips and perioral lines

Marionette lines

Labiomental fold

Neck

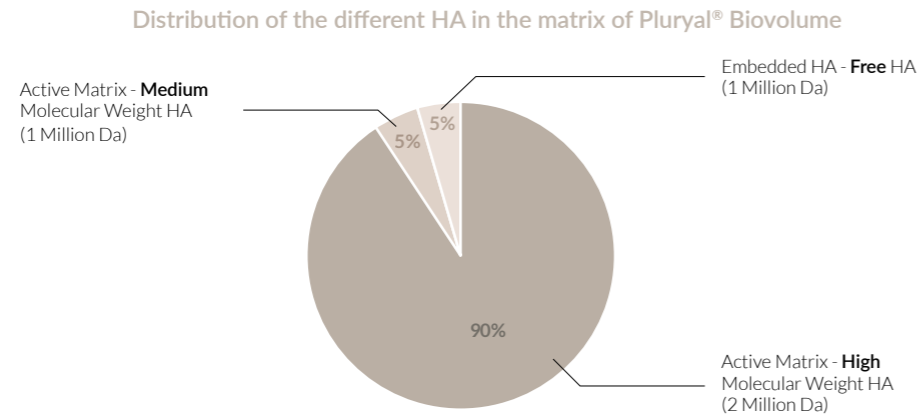
PLURIAL[®] BIOVOLUME

STRONG BIOFILLER

Pluryal[®] BIOVOLUME is an injectable medical device based on the **MATRICIAL 3D TECHNOLOGY[®]**. It is a safe, sterile, transparent, apyrogenic, physiological and bio-resorbable-over-time gel.

It targets the **deep loss of volume, skin sagging and deep wrinkles**.

Composition: 25 mg/ml of hyaluronic acid, including 5% free hyaluronic acid embedded in the 3D matrix.



Other ingredients: Phosphate buffer, NaCl

Cross linking: ++++ (BDDE < 0.1 ppm)

Extrusion Force (N): 30

G' factor (mPa): 200,000

Sterilization: Steam

Endotoxins (EU/mL): < 20

Indications

Treatment of imperfections that require an enrichment of the facial tissue with volumetric increase.

1. Deep loss of volume, deep wrinkles
2. Deep skin sagging
3. Skin quality

Volumetric action

The product physiologically restores the volumes

Re-structuring action

Improvement of tissues through cell receptor stimulation

Moisturizing action

Re-integrates the natural osmolarity of tissues

Level of Injection: Deep dermis / Superficial hypodermis

Maintenance treatment: Every 8-12 months or as required

Pack Contents: 1 x 1 ml pre-filled syringes | 23G x 19 mm needle | 25G x 38 mm cannula

Regulatory: Syringe (CE 0373, MD Skin Solutions) | Needles (CE 0123, TSK)

PLURIAL[®] BIOVOLUME

STRONG BIOFILLER

TARGET AREAS



Temples

Cheeks

Deep skin flaccidity

Nasolabial folds
/Bitterness lines

Lips

Jaw line/Mandibular contour

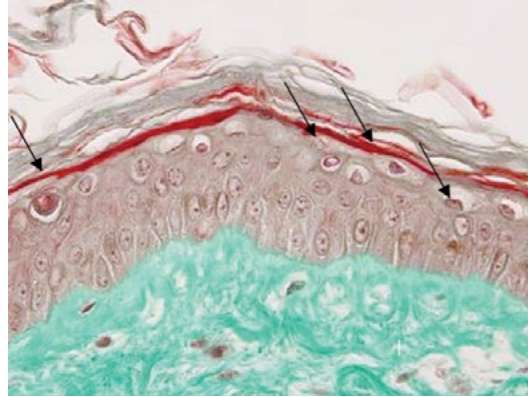
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CLINICAL PROVEN EFFICACY OF THE BIOSTIMULATING EFFECT

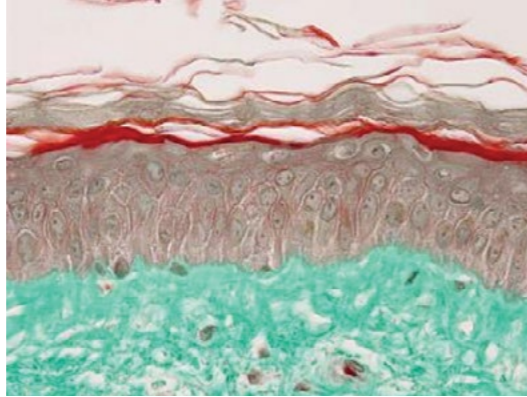
EX-VIVO STUDIES^[11] (SKIN EXPLANTS)

1. **Cell viability control** (Examination of the general cell and tissue morphology by Masson trichrome staining)

Control at Day 9



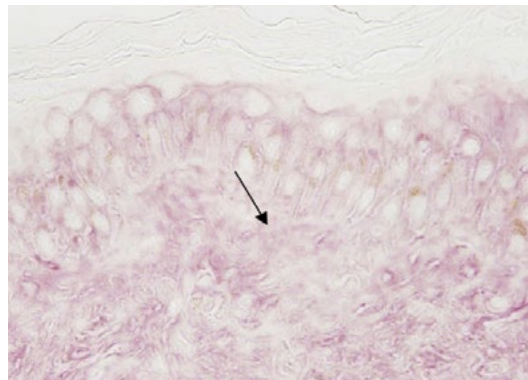
Matricyal 3D Technology® (Pluryal® Biosculpture) at Day 9



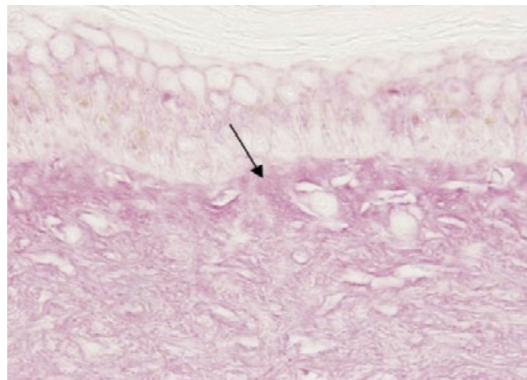
Matricyal 3D Technology® improves epidermal viability without altering dermal viability. It protects and strengthens the epidermis, as well as provides it with a higher resistance capacity to offset the slight alterations due to the test.

2. **Activity related to hyaluronic acid** (evaluation of the expression of hyaluronic acid in the papillary dermis after HABP labelling)

Control at Day 9



Matricyal 3D Technology® (Pluryal® Biosculpture) at Day 9

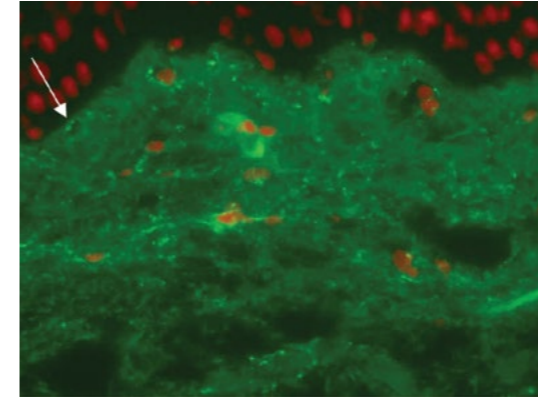


Matricyal 3D Technology® improves the quantity of hyaluronic acid in the upper papillary and reticular dermis.

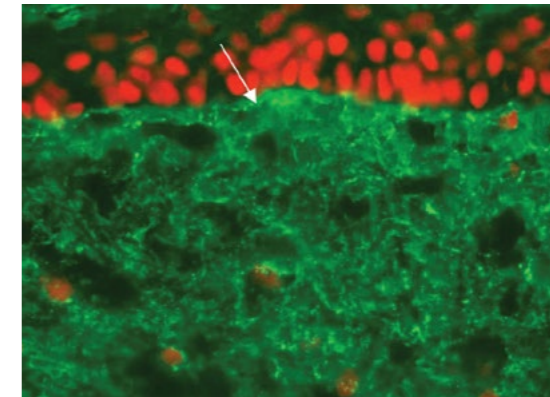
CLINICAL PROVEN EFFICACY OF THE BIOSTIMULATING EFFECT

3. **Activity related to fibronectin** (Evaluation of the expression of fibronectin in the dermis after fluorescence immunolabelling)

Control at Day 9



Matricyal 3D Technology® (Pluryal® Biosculpture) at Day 9



Fibronectin is a structural protein found in the extracellular matrix. It is one of the ligands contained in integrins. Fibronectin plays various biological roles in the skin: it represents a growth factor, an adhesion molecule, as well as a chemotactic agent for fibroblasts^[12] and it contributes to collagen fibril deposition and assembly. In addition, it controls the migration of keratinocytes in the skin's healing process.^[13]

Fibronectin stimulates fibroblasts and is involved in the collagen network restructuring in the extracellular matrix. Immunolabelling of fibronectin shows that the greener fluorescence there is, the more fibronectin there is.

NB: in red, nuclei counterstain to spot cells.

Matricyal 3D Technology® improves the quantity of fibronectin in the upper papillary and reticular dermis.

CLINICAL PROVEN EFFICACY

IN-VIVO STUDY (CLINICAL CASES)

CASE 1:

Before

After



Treatment: Lip Augmentation
Product: Pluryal® BIOCLASSIC
Courtesy of Dr. Nina KOLOT, Dermatology, Ukraine

CASE 2:

Before

After



Treatment: Nasolabial folds
Product: Pluryal® BIOCLASSIC
Courtesy of Dr. Nina KOLOT, Dermatology, Ukraine

CASE 3:

Before

After



Treatment: Neck wrinkles
Product: Pluryal® BIOCLASSIC
Courtesy of Dr. Anastasiia RUBAN, Dermatology, Ukraine

CASE 4:

Before

After



Treatment: Modelling of the jawline
Product: Pluryal® BIOVOLUME
Courtesy of Dr. Anastasiia RUBAN, Dermatology, Ukraine

CLINICAL PROVEN EFFICACY

CASE 5:

Before

After



Treatment: Modelling of the chin
Product: Pluryal® BIOVOLUME
Courtesy of Dr. Anastasiia RUBAN, Dermatology, Ukraine

CASE 6:

Before

After



Treatment: Cheeks, Jowls, Marionette lines and Flaccidity
Product: Pluryal® BIOCLASSIC + Pluryal® BIOVOLUME
Courtesy of Dr. Katerina LYKKA, Dermatology, Greece

CASE 7:

Before

After



Treatment: Chin, Jawline, Nasolabial folds and Skin quality
Product: Pluryal® BIOCLASSIC + Pluryal® BIOVOLUME
Courtesy of Dr. Marina DISTELDORFF, Dermatology, Luxembourg

20 times less BDDE*

1/3 less BDDE than regular fillers*

*than the limit authorized by the European and American regulations and at least 1/3 less than regular dermal fillers composed of hyaluronic acid



Pluryal® BIOCLASSIC and Pluryal® BIOVOLUME are a class III medical device which must only be used by doctors who have received specific training on intradermal injection techniques. Read the instructions before use. Inform the patients about possible side effects.

Sources:

- ¹Maytin E. V. (2016). Hyaluronan: More than just a wrinkle filler. *Glycobiology*, 26(6), 553–559.
- ²Jiang, L., Liu, G., Liu, H., Han, J., Liu, Z., & Ma, H. (2018). Molecular weight impact on the mechanical forces between hyaluronan and its receptor. *Carbohydrate polymers*, 197, 326–336.
- ³Wolny, P. M., Banerji, S., Gounou, C., Brisson, A. R., Day, A. J., Jackson, D. G., & Richter, R. P. (2010). Analysis of CD44-hyaluronan interactions in an artificial membrane system: insights into the distinct binding properties of high and low molecular weight hyaluronan. *The Journal of biological chemistry*, 285(39), 30170–30180.
- ⁴Bodo, M., Pezzetti, F., Baroni, T., Carinci, F., Arena, N., Nicoletti, I., & Becchetti, E. (1993). Hyaluronic acid modulates growth, morphology and cytoskeleton in embryonic chick skin fibroblasts. *The International journal of developmental biology*, 37(2), 349–352.
- ⁵Cohen, J. L., Dayan, S. H., Brandt, F. S., Nelson, D. B., Axford-Gatley, R. A., Theisen, M. J., & Narins, R. S. (2013). Systematic review of clinical trials of small- and large-gel-particle hyaluronic acid injectable fillers for aesthetic soft tissue augmentation. *Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al.]*, 39(2), 205–231.
- ⁶Landau M, Fagien S. Science of Hyaluronic Acid Beyond Filling: Fibroblasts and Their Response to the Extracellular Matrix. *Plast Reconstr Surg*. 2015 Nov;136(5 Suppl):188S-195S.
- ⁷Lesley, J., Hascall, V. C., Tammi, M., & Hyman, R. (2000). Hyaluronan binding by cell surface CD44. *The Journal of biological chemistry*, 275(35), 26967–26975. <https://doi.org/10.1074/jbc.M002527200>
- ⁸Jaime M. Cyphert, Carol S. Trempus, Stavros Garantziotis, "Size Matters: Molecular Weight Specificity of Hyaluronan Effects in Cell Biology", *International Journal of Cell Biology*, vol. 2015, Article ID 563818, 8 pages, 2015.
- ⁹Litwiniuk, M., Krejner, A., Speyrer, M. S., Gauto, A. R., & Grzela, T. (2016). Hyaluronic Acid in Inflammation and Tissue Regeneration. *Wounds: a compendium of clinical research and practice*, 28(3), 78–88.
- ¹⁰Neuman, M. G., Nanau, R. M., Oruña, L., & Coto, G. (2011). In vitro anti-inflammatory effects of hyaluronic acid in ethanol-induced damage in skin cells. *Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques*, 14(3), 425–437.
- ¹¹Evaluation de l'action de différents produits injectables (Pluryal Densify, Pluryal Biosculpture, Pluryal Silk) à partir d'explants de peau humaine ex vivo», Study 19E4548, conducted by the BIO-EC laboratory.
- ¹²Akiyama et al., *The journal of Cell Biology*. 1989. 109: 863-875; Bitterman et al., 1983. *The Journal of Cell Biology*. 97: 1925-1932
- ¹³Larjava et al., 2002. *Cell invasion*. 3: 42-64

Pluryal is a registered trademark of MD Skin Solutions.



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PBF_BRO_PRO_EN_RevA