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natural growing, natural healing

Summary Safety Clinical Performance

COLLAGEN POWDER VIALS, STERILE

SSCP revision number	Date issued	Change description	Approved by RA
Rev.00	23/09/2024	First release	

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FOR HEALTHCARE PROFESSIONALS

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients. The following information is intended for healthcare professionals.

1. Device identification and general information

The medical device COLLAGEN POWDER VIALS, STERILE is a non-active medical device, implantable, sterile and mono-use, that appears as a powder of heterologous equine collagen type I, contained in a glass vial, closed with a plastic cap and an aluminum ferrule.

The injectable collagen powder is designed to be injected into the deep dermis, in conditions where the tissue has lost its physiological characteristics, its volume and its mechanical characteristics.

The medical device is available in:

- Cartbox with three 70 mg glass vials of device;

Device trade name: NITHYA

Manufacturer's name and address: EURORESEARCH S.r.l. – Corso Venezia, 5 – 20121, Milano (MI)

Manufacturer's single registration number (SRN): IT-MF-000038084

Basic UDI-DI: 805495340CPVMM

Medical device nomenclature description terms/EMDN: P900402, RESORBABLE FILLING AND RECONSTRUCTION DEVICES

Class of device: III (Class D for Arabian registration)

Year when the first certificate (CE) was issued covering the device: The medical device was first CE marked on December 5th, 2013.

Authorised representative if applicable; name and the SRN: n.a

NB's name (the NB that will validate the SSCP) and the NB's single identification number: ISTITUTO SUPERIORE DI SANITA' – 0373.

2. Intended use of the device

Intended purpose

The device is intended for injection into the deep dermis to correct the deep facial cutaneous sagging (chrono and photo aging signs).

Intended user/intendend patient population/clinical condition

The medical device should be used only by healthcare professionals on adult population of both genders, in clinical applications such as face volume and contour restoration; correction of nasolabial folds and wrinkles around the eyes.

When for various reasons the physiology or the mechanical characteristics of the dermis are altered, not only the dermal tissue is affected but also the overlying epidermis (to which the dermis offers mechanical and functional support), with a general impairment of the health of the skin. At a clinical and functional level, alterations in the physiology of the dermis leads to a decrease in fibroblastic activity, slowdown in collagen turnover, decrease in the level of hydration, drops in elastin levels, general loss of volume and skin atrophy. On a macroscopic level, these condition cause loss of tissue volume, thinning of the dermal layer, skin relaxation, wrinkling (particularly in the face area), excess skin in the upper and lower eyelids, prominence of the nasolabial folds, ptosis of the forehead.

The physiological skin aging process also leads to alterations of dermal physiology its mechanical and structural characteristics of the dermis, with collagen fibres becoming less stable and resistant over time and fibroblasts reducing their activity so that the turn-over between old and new collagen slows down.

Environmental factors such as exposure to UV rays, prolonged exposure to heat and pollution accelerate skin aging. Prolonged states of oxidative stress can cause structural alterations of the dermis, as free radicals can attack collagen, favouring cross-links between the fibers that become less elastic and less resistant, leading in the long term to a loss of tissue tone.

Finally, the psychological implications of the clinical conditions described above should not be underestimated. Given the direct impact on people's outward appearance, patients often begin to suffer from low self-esteem and low self-esteem.

Indications

The medical device is indicated for:

- face volume and contour restoration;
- correction of nasolabial folds and wrinkles around the eyes.

Contraindications

- Do not inject the product in the eyelids or in the glabellar area (forehead) and in the oral/perioral region.
- Do not inject into blood vessels (intravascular use).

DO NOT USE THE PRODUCT:

- In patients with vascular collagen diseases or autoimmune connective tissue disorders (connectivopathies);
- In patients with epilepsy not controlled by medications;
- In patients prone to develop hypertrophic scars;
- In patients with known hypersensitivity to collagen;
- In patients with porphyria;
- During pregnancy or breast-feeding;
- In children;
- On skin areas affected by inflammation and/or active Infection (acne, herpes, etc.);
- In immediate association with laser treatments, deep chemical peels or dermabrasion. In case of a superficial peel, injection is not recommended if a significant inflammatory reaction is present.

3. Device description

The medical device COLLAGEN POWDER VIALS, STERILE is a non-active medical device, sterile and mono-use, that appears as a powder of heterologous equine collagen type I, contained in a glass vial, closed with a plastic cap and an aluminum ferrule.

The powder appears as a homogenous and fine powder, with an ivory white colour.

The device is supplied as sterile, and sterilization is performed by gamma ray irradiation (irradiation dose 25 kGy).

The injectable collagen powder is designed to be injected into the deep dermis, in conditions where the tissue has lost its physiological characteristics, its volume and its mechanical characteristics.

The medical device is available in:

- Cartbox with three 70 mg glass vials of device;

The only constituent of the device COLLAGEN POWDER VIALS, STERILE is Collagen type I, extracted from equine tendons.

A reference to previous generation(s) or variants if such exist, and a description of the differences.

The medical device was EC certified on 05/12/2013 according to Annex V of the Directive 93/42/EEC and subsequent amendments and / or additions regarding approval of quality assurance system for production and/or sterilization (certificate number CTPQPZ-1660082-135, issued by Istituto Superiore di Sanità) and then on 26/03/2014 according to Annex III of the Directive 93/42/EEC and subsequent amendments and / or additions regarding EC type examination (certificate number CTP-1082-15, issued by Istituto Superiore di Sanità).

The medical device was then recertified on 01/10/2018 according to Annex II, excluding 4, of the Directive 93/42/EEC and subsequent amendments and / or additions regarding EC declaration of conformity full quality assurance system (certificate number QCT-0098-18, issued by Istituto Superiore di Sanità) and then on 05/11/2019 according to Annex II, including 4, of the Directive 93/42/EEC and subsequent amendments and / or additions regarding EC design-examination certificate (certificate number EPG-0254-19, issued by Istituto Superiore di Sanità).

The transition to MDR 2017/745 certification did not involve any changes to the product design

Description of any accessories which are intended to be used in combination with the device:

Not applicable. The device has no accessories.

Description of any other devices and products which are intended to be used in combination with the device:

The medical device has to be injected with a common CE-marked fine injection needle with a size of 30G in the deep derma.

4. Risks and warnings

Residual Risks and side effects

The analysis of the overall residual risk compared with the acceptability ranking defined in the Risk Management Plan is acceptable and none of the mitigation actions have introduced a new risk. Furthermore, each residual risk does not exceed the expected benefit to the patient.

It can be concluded that the overall residual risk is balanced by the benefits brought by the use of the product resulting in a favorable risk/benefit ratio.

Side effects

The product is hypoallergenic. No side effects associated with the product have been reported. Patients should be informed of potential side effects secondary to administration of this medical device by means of injection; these might appear immediately or some time after administration. They include (but are not limited to):

- Slight stinging sensation, which disappears in a few minutes;
- Inflammatory reactions (such as redness, swelling, edema, erythema, etc.), sometimes in conjunction with itching, or pain to touch, or both. These reactions can last up to one week;
- Bruises/Hematomas;
- Hardening or nodules at the injection site;
- Coloration or discoloration of the treated area;
- Cases of necrosis of the glabellar region, abscess, granuloma, and immediate or delayed hypersensitivity after collagen injections have been described in the literature. It is therefore imperative to take these potential risks into account;
- Inflammatory reactions lasting longer than a week or other side effects must be immediately reported by patients to their practitioner, who will provide adequate treatment to eliminate such reactions.

Any other undesirable side effect associated with injection of NITHYA must be reported to the distributor and/or manufacturer.

Warnings and precautions

- Before starting the treatment, the patient should be informed of the device's indications and contraindications, as well as of its incompatibilities and possible adverse effects. As with any other intracutaneous treatment, the product may pose a risk of infection.
- Before injecting, thoroughly disinfect the area to be treated. The usual precautions for intradermal infiltrations should be observed.
- Inject slowly. Failure to comply with these precautions may lead to needle detachment and/or product leakage in the Luer lock area.
- The amount of injected product will depend on the area to be treated.
- After injection, it is important to massage the treated area to evenly spread the product. - Do not use in case of known individual hypersensitivity to the product.
- Do not inject in skin areas with active infection or inflammation.
- The product is not recommended during pregnancy and breast-feeding, although specific contraindications are not known.
- The physician's technical ability is essential for the treatment's success, therefore this medical device should only be administered by physicians who have received specific training in injectables.

- Altering the product or using it in any way that is not in accordance with the conditions of use described in this document may affect its sterility and performance, which will not be guaranteed any longer.
- Make sure that the package and the glass vial are intact before use. The product is for single use; do not reuse any remaining solution after its first opening. Quality and sterility can be guaranteed only for vials / packages sealed at the origin.
- Dispose of this product responsibly after use.
- Please check the product's expiry date and do not use it after it has expired.

KEEP THIS MEDICINE OUT OF THE SIGHT AND REACH OF CHILDREN INTERACTIONS

There are no known interactions with other substances.

Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN):

- No safety findings requiring close monitoring were identified
- No FSCA has been identified

5. Summary of clinical evaluation and post-market clinical follow-up (PMCF)

Post Market Clinical Follow-up show that the well-known clinical behaviour of the devices for which the medium/long term clinical performance and safety is already known from the use of similar products.

Summary of clinical data related to equivalent device:

The demonstration of equivalence was carried out according to MDCG 2020-5 provisions in which technical, biological and clinical characteristics shall be considered when demonstrating equivalence to another device.

- Technical characteristics: The device is of similar design; is used under similar conditions of use; has similar specifications and properties including physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and software algorithms; uses similar deployment methods, where relevant; has similar principles of operation and critical performance requirements.

- Biological characteristics: The device uses the same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables.

- Clinical characteristics: The device is used for the same clinical condition or purpose, including similar severity and stage of disease, at the same site in the body, in a similar population,

including as regards age, anatomy and physiology; has the same kind of user; has similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.

The characteristics listed above shall be similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device. Considerations of equivalence shall be based on proper scientific justification.

According to above criteria the following products available on the market were assessed.

- Evolence: It is a porcine- based collagen dermal filler intended for correction of wrinkles and nasolabial folds. It is available as prefilled syringes. It can not be considered an equivalent device in terms of technical and biological characteristics since has different deployment method (ready to use product and not be diluted before use) and different collagen animal source and these differences are clinically significant.

- Dermicol-P35: It is a porcine-based collagen dermal filler intended for dermal rejuvenation and/or restoration of the skin in various sites, including acne scars, cheeks, hands, lips, nose and tear troughs and for correction of nasolabial folds. It is supplied in a prefilled syringe. It can not be considered an equivalent device in terms of technical and biological characteristics since has different deployment method (ready to use product and not be diluted before use) and different collagen animal source and these differences are clinically significant.

- Cosmoderm, Cosmoplast: They are human-based collagen implants intended for the correction of soft tissue contour deficiencies, such as wrinkles and acne scars. They are supplied in individual treatment syringes packed with sterile needles, ready for use. They can not be considered equivalent devices in terms of technical and biological characteristics since have different deployment method (ready to use products and not be diluted before use) and different collagen source and these differences are clinically significant.

- Zyderm/Zyplast: They are bovine-based collagen implants (bovine collagen dispersed in physiological saline buffered with phosphate containing 0.3% lidocaine) intended for the correction of soft tissue contour deficiencies, such as wrinkles. They are supplied in prefilled syringes, ready for use. They can not be considered equivalent devices in terms of technical and biological characteristics since have different deployment method (ready to use products and not be diluted before use) and different collagen animal source and ingredients and all these differences are clinically significant.

- Guna Collagen Medical Devices (MD-TISSUE H): It is equine-base collagen (equine collagen extract – excipients: Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection) implant intended to limit the physiological deterioration of the skin and subcutaneous connective tissue, and counterbalance the effects of chrono-ageing and photo-ageing. It is a suspension ready to be injected that does not need to be reconstructed. It is ready for use. It can not be considered equivalent device in terms of technical and biological characteristics since have different deployment method (ready to use products and not be diluted before use) and different collagen animal source and excipients and all these differences are clinically significant.

All above listed products can not be considered substantially equivalent devices according to MDCG 2020-5 provisions. Therefore, no device is deemed relevant to discuss in terms of equivalence with Nithya in this Clinical Evaluation Report. The above ones can be considered only as similar devices to Nithya.

The collected data and analyzed through the clinical evaluation demonstrated that similar devices

and products containing collagen are well-known in terms of clinical behaviour and have a good level in terms of medium/long term clinical performance and safety.

Summary of clinical data from conducted investigations of the device:

The medical device has been tested in a clinical investigation conducted in several clinical centres and hospitals in Italy, on a statistically significant medical population.

The results of the clinical investigation have been published in 2017 on the international scientific specialistic magazine "*Journal of Clinical & Experimental Dermatology Research*". The study is summarized here below reporting the main information. The full article reporting all the details on the study is attached to the clinical evaluation report.

- *Anti-Age Activity and Tolerance Evaluation of Collagen Micro-Injection Treatment Associated to Topical Application of a Cosmetic Formulation (Investigator-Initiated Multicentre Trial) - Sparavigna A, Tateo A, Inselvini E, Tocchio M, Orlandini MC, Botali G. - J Clin Exp Dermatol Res, an open access journal Volume 8 Issue 3 2017*

This multicenter study was conducted to evaluate the efficacy and safety of injectable collagen powder in the treatment of signs of skin chrono- and photo-ageing. The study involved 72 female patients aged 40 to 65 years who were treated with 70 mg of injectable collagen powder. The product was administered at the first examination, after two weeks (T1) and after another two weeks (T2). Patients were followed in total for 6 months. All the clinical parameters monitored, i.e. the assessment of wrinkle severity (WSRS), the facial volume loss scale (FVLS) and the degree of wrinkles in the area surrounding the eyes, showed improvements at each follow-up visit. Profilometry further confirmed the results. Patients were also asked to complete a questionnaire on treatment satisfaction and all patients gave positive feedback. In particular, 95% pointed to an improvement in face volume, surface wrinkles and a greater softness of the face.

Injectable collagen powder has been tested for the treatment of dermal hypotrophy at a dosage of 200 mg in 152 patients aged 35 to 65 years. Efficacy has been assessed as skin hydration, tissue texture, skin firmness and radiance. There was no deterioration in the values considered and the parameters improved in most patients.

Daily clinical experience in the use of injectable collagen powder was then collected on 20 female patients, treated with a 70 mg injection of injectable collagen powder and monitored for 4 months. Treatments were effective in improving tissue quality of the treated area.

Again from daily medical experience, regarding the use of injectable collagen on about 40 female patients, it has been shown that the treated areas showed an increase in compactness and an improvement in the structure and quality of the tissue, as well as the fact that collagen promotes neovascularization of the treated area.

Summary of clinical data from other sources:

The evaluation of clinical safety and efficacy was performed based, not only on the clinical investigation above, but also on data collected from these sources:

Pre-clinical studies:

In order to assess and validate the safety profile of the product before starting to collect clinical data on the human use, the manufactured conducted a Biological Evaluation of the medical device in accordance with ISO 10993 - 1 'Biological evaluation of medical devices - Part 1: Evaluation and Testing". The relevant biocompatibility tests performed on the product are summarized here below:

- Delayed hypersensitisation test on guinea pigs (15 treated and 5 control guinea pigs)
- Rabbit skin irritation test (3 rabbits treated)
- Cytotoxicity test for direct contact with mammalian fibroblasts (ATCC BalbC 3T3 cells)

Tests have shown that the product is neither sensitising nor irritating to the skin and is not cytotoxic. It should also be noted that the skin irritation test was conducted with 400 mg of collagen powder, a dosage twice as high as the maximum available on the market today.

- Acute systemic toxicity test (5 treated and 5 control mices)
- Subacute toxicity test (10 treated and 10 control rats)
- Subcutaneous implantation test (10 treated and 10 albino rats).

Tests have shown that the product does not cause neither toxic symptoms neither systemic toxicity. Moreover, the product causes slight local effects.

The following biocompatibility tests have also been conducted on collagen when formulated as a sterile pad.

- Cytotoxicity by elution on murine fibroblasts (NCTC cells L929)
- Salmonella Typhimurium Mutagenicity Test (Ames test)
- Allergic sensitization on guinea pigs (20 treated guinea pigs + 10 control guinea pigs)
- Skin irritation on rabbit (3 treated albino rabbits)

Even if it is a different presentation (sterile pad), the substance tested is the same (pure collagen type I extracted from horse tendons): these data are therefore to be considered in support of the safe use.of collagen. The results showed that the product is not cytotoxic, nor mutagenic, nor sensitising and is not irritating to the skin.

Clinical experiences:

Further to the clinical trial published, the manufacturer has collected and analysed the clinical experiences of several physicians as concerns the use of the medical device according to the intended use (***Clinical* experience 1, *2; 3***).

The above-mentioned clinical data are summarised below:

1. *Dermal biostimulation by heterologous type I collagen - Prof. Andrea Corbo*
2. *Clinical Experience with Nithya - Spontaneous statement by Dr. Adolfo Gasparetto, Dermatika outpatient clinic in Granze (Padua) - 31 October 2018*
3. *Clinical Experience with Nithya - Spontaneous Statement by Dr. Antonello Tateo, TBClinic Aesthetic Clinic in Pavia - 20 January 2019*

In total, clinical trial and experiences involved about 240 patients and the data collected on these patients confirmed the efficacy of injectable collagen powder.

These clinical data are further supported by the data coming from the market. The device is on the market since 2014 in several countries, both in EU and extra-EU; more than 140000 vials have been globally sold and no complaints on efficacy have ever been reported.

In addition to the described clinical data, the manufacturer has set up a Postmarketing Clinical Follow-up Plan (PMCF plan), which involves collecting and analyzing information from the market and planning an additional clinical study to confirm the safety and efficacy of the product.

Post-marketing surveillance:

The Manufacturer monitors the safety and the efficacy of the product through the post-marketing surveillance, in particular through:

- Product-specific bibliographic research, performed according to the Manufacturer internal procedure, including the evaluation of any incidents on similar products/material
- Vigilance system;
- Analysis of complaints;
- Annual review of risk analysis;

Since the product launched up today there were no serious adverse events (SAEs) received by the company, No cases were reported in association with the trade name product.

An overall summary of the clinical performance and safety

The safety claims of the device are considered fully supported on the basis of the biocompatibility data showing not cytotoxic, mutagenic, irritating, sensitizing, toxicity and implant issues related to collagen, on the basis of the safety data retrieved from the literature and on the basis of the performed clinical study.

The efficacy claims of the device are considered fully supported on the basis of the retrieved clinical data.

The risk/benefit profile of the medical device was estimated. The estimate considered the result of the risk analysis and efficacy assessment. The identified residual risks appear to be under control if the device is used for its intended purpose and in accordance with the instructions provided and the warnings given. The warnings provided help to prevent misuse and mishandling of the product.

The benefit is proven by the evidence provided, so the risk/benefit profile is acceptable.

As a further confirmation, experience in the commercialization of the device supports the benefit/risk ratio considerations.

***Ongoing or planned post-market clinical follow-up*:**

A post marketing clinical follow up has been planned to confirm the data of efficacy already know on the formulation.

6. Possible diagnostic or therapeutic alternatives

Injectable collagen powder is designed to act where dermis and connective tissue are damaged, with reduced volume and loss of physiological characteristics. These conditions also impact the overlying skin, which tends to lose its structural characteristics and become more fragile and thinner.
There are several therapies used in clinical practice for the resolutions of the above conditions; to choose the most appropriate therapy, it is always necessary to take into consideration a number of variables, such as the size of the area to be treated, the specific condition of the area to be treated, the patient's general health status, and the patient's medical history. Since these are also treatments for conditions that by their very nature also have aesthetic implications, it is important that the patient is also properly informed of the aesthetic effect that the treatment may or may not have.

Among the most common therapies for correction the deep facial cutaneous sagging (chrono and photo aging signs) there are "dermal fillers." These are products designed to be injected directly into the dermis, where they help restore tissue physiology.
Conceptually, these products can act in two ways: "passively," i.e., acting as simple filler agents, or "actively," i.e., promoting and supporting the recovery of physiological functions of the tissue.
Passive fillers therefore have only a structural role, restoring tissue volume to optimal levels. In this case, there are no biorestoration effects and the effect is mainly cosmetic: the tissue regains texture and volume but does not recover its normal physiology. Usually these products are not biodegradable or poorly biodegradable and are therefore presented as permanent treatments. Common passive dermal fillers are silicone and polymethylmethacrylate.

Other fillers, on the other hand, have an active role, that is, they do not just restore tissue volume, but their main action is to stimulate tissue activity so that normal tissue physiology is restored. Most of these products biodegrade over time. Euroresearch's injectable collagen powder falls into this category of products; other common products include hyaluronic acid fillers, calcium hydroxyapatite, and poly-lactic acid.

Peeling is another widely used therapy. Peeling is based on the principle that damage to the epidermis and dermis itself can naturally stimulate fibroblastic activity. In fact, it is known that the inflammatory response following damage stimulates the deposition of new collagen; consequently, controlled damage leads to the production of new collagen and tissue revitalization. Over the years, peeling has been performed by various methods, using either chemical agents (e.g., phenol, trichloroacetic acid) or physical agents (e.g., dermabrasion, microdermabrasion, or laser) or combining chemical and physical agents. The main risk of this technique is related to the fact that the damage done to the tissue is too incisive and that in the long run there may be problems, primarily excessive thinning of the skin. In addition, excessive damage could stimulate more fibrosis at the expense of new collagen deposition with repercussions on the effectiveness of the treatment.

Lifting is another widely used therapy. These surgical treatments have been studied to correct some specific defects of face, focusing only on the aesthetic aspect of the loss of functionality of the dermis and epidermis. These treatments therefore aim to restore the "youthful" appearances of the tissue, without promoting the restoration of the tissues themselves.

They present all the potential risks associated with surgical operations (bleeding, infections, long recovery times).

Another alternative is represented by Botulinum.

Botulinum has an effect on wrinkles and facial skin as it acts on the underlying muscle contractions. Injection of botulinum toxin into the muscles under facial wrinkles causes relaxation of those muscles, resulting in the smoothing of the overlying skin. Several commercial products are available on the market, classified as drug product. The safety of this treatments is well known however adverse events can occur. Side effects include headaches, flu-like symptoms, and allergic reactions; furthermore in case the toxin is injected into the wrong muscle group or with time spread from the injection site, it may cause temporary paralysis of unintended muscles causing partial facial paralysis or muscle weakness. These symptoms may last for weeks. This is the reason why in 2009, the US FDA announced that boxed warnings would be added to available botulinum toxin products, warning of their ability to spread from the injection site.

Botulinum is generally administered in outpatients care and no specific recovery times are required after the treatment. The effect is not permanent, and treatments should be regularly repeated to prolong the effect.

However, the treatment is limited to the external and aesthetic aspects only, without treating the primary causes of the situation. This means that it is not possible to reach a recovery of the physiological properties of the tissue and there is no direct action at dermal level.

Therefore, the medical device falls into a framework of established medical treatments.

To summarize: Collagen powder injections present similar benefits and less risks when compared to therapeutic alternatives.

7. Suggested profile and training for users

The product must be administered by healthcare professionals only. The physician's technical ability is essential for the treatment's success, therefore this medical device should only be administered by physicians who have received specific training in injectables

8. Reference to any harmonised standards and CS applied

MDCG-2019-9

2017/745 MDR, Annex I, 23.1 (a) 89 MDR, Article 8 (2)

PATIENTS

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The information presented below is intended for patients.

A more extensive summary of its safety and clinical performance prepared for healthcare professionals is found in the first part of this document.

The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an Implant card or the Instructions For Use to provide information on the safe use of the device.

1. Device identification and general information

The medical device COLLAGEN POWDER VIALS, STERILE is a non-active medical device, implantable, sterile and mono-use, that appears as a powder of heterologous equine collagen type I, contained in a glass vial, closed with a plastic cap and an aluminum ferrule.

The injectable collagen powder is designed to be injected into the deep dermis, in conditions where the tissue has lost its physiological characteristics, its volume and its mechanical characteristics.

The medical device is available in:

- Cartbox with three 70 mg glass vials of device;

Device trade name: NITHYA

Manufacturer's name and address: EURORESEARCH S.r.l. – Corso Venezia, 5 – 20121, Milano (MI)

Basic UDI-DI: 805495340CPVMM

Year when the first certificate (CE) was issued covering the device: The medical device was first CE marked on December 5th, 2013.

2. Intended use of the device

Intended purpose

The device is intended for injection into the deep dermis to correct the deep facial cutaneous sagging (chrono and photo aging signs).

Intended user/intendend patient population/clinical condition

The medical device should be used only by healthcare professionals on adult population of both genders, in clinical applications such as face volume and contour restoration; correction of nasolabial folds and wrinkles around the eyes.

When for various reasons the physiology or the mechanical characteristics of the dermis are altered, not only the dermal tissue is affected but also the overlying epidermis (to which the dermis offers mechanical and functional support), with a general impairment of the health of the skin. At a clinical and functional level, alterations in the physiology of the dermis leads to a decrease in fibroblastic activity, slowdown in collagen turnover, decrease in the level of hydration, drops in elastin levels, general loss of volume and skin atrophy. On a macroscopic level, these condition cause loss of tissue volume, thinning of the dermal layer, skin relaxation, wrinkling (particularly in the face area), excess skin in the upper and lower eyelids, prominence of the nasolabial folds, ptosis of the forehead.

The physiological skin aging process also leads to alterations of dermal physiology its mechanical and structural characteristics of the dermis, with collagen fibres becoming less stable and resistant over time and fibroblasts reducing their activity so that the turn-over between old and new collagen slows down.

Environmental factors such as exposure to UV rays, prolonged exposure to heat and pollution accelerate skin aging. Prolonged states of oxidative stress can cause structural alterations of the dermis, as free radicals can attack collagen, favouring cross-links between the fibers that become less elastic and less resistant, leading in the long term to a loss of tissue tone.

Finally, the psychological implications of the clinical conditions described above should not be underestimated. Given the direct impact on people's outward appearance, patients often begin to suffer from low self-esteem and low self-esteem.

Indications

The medical device is indicated for:

- face volume and contour restoration;
- correction of nasolabial folds and wrinkles around the eyes.

Contraindications

- Do not inject the product in the eyelids or in the glabellar area (forehead) and in the oral/perioral region.
- Do not inject into blood vessels (intravascular use).

DO NOT USE THE PRODUCT:

- In patients with vascular collagen diseases or autoimmune connective tissue disorders (connectivopathies);
- In patients with epilepsy not controlled by medications;
- In patients prone to develop hypertrophic scars;
- In patients with known hypersensitivity to collagen;
- In patients with porphyria;
- During pregnancy or breast-feeding;
- In children;
- On skin areas affected by inflammation and/or active Infection (acne, herpes, etc.);
- In immediate association with laser treatments, deep chemical peels or dermabrasion. In case of a superficial peel, injection is not recommended if a significant inflammatory reaction is present.

3. Device description

Device description and material/substances in contact with patient tissues

The medical device COLLAGEN POWDER VIALS, STERILE is a non-active medical device, sterile and mono-use, that appears as a powder of heterologous equine collagen type I, contained in a glass vial, closed with a plastic cap and an aluminum ferrule.

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The medical device is available in:

- Cartbox with three 70 mg glass vials of device.

The only constituent of the device COLLAGEN POWDER VIALS, STERILE is Collagen type I, extracted from equine tendons.

Description of how the device is achieving its intended mode of action

Mode of action:

The medical device supplies collagen directly into the weakened area at the level of the dermis, the layer responsible for the texture, resistance and elasticity of the skin, placed under the epidermis. Thanks to its mechanical properties, collagen contributes to the restoration of the structural and functional characteristics of the dermis and creates a micro-environment suitable for anchoring the

fibroblasts, which in turn contribute to the restoration of the normal physiology of the dermis by also producing collagen.

The medical device acts as a dermic bio-revitalizer and not as a filler. It does not remain in the application site for prolonged time lengths to give volume to the treated area. The device promotes the natural proliferation of fibroblasts, the revitalization of the natural conditions of the derma and the degradation does not constitute a problem in this action. Furthermore, the collagen contained in the medical device is not crosslinked, therefore it is more incline to degradation: depending on the specific conditions of the treated area, it is possible that the medical device degrades in faster time lengths and literature reports that collagen can degrade in brief time, not more than 4 weeks.

Collagen is one of the most important structural and biological components of the body. It is a structural protein with minimal immunoreactivity that plays structural roles in the skin, connective tissue, bone, and teeth. Collagen constitutes 75% of the dry weight and 18-30% of the volume of the dermis and gives it strength, resistance, and elasticity.

Collagen and collagen-based materials are widely used for medical applications, such as scaffold construction in tissue engineering, injections, solid constructs from solution and decellularized matrices. It also has efficacy in the treatment of chronic wounds, burn, venous and diabetic ulcers. Thanks to its high strength, it is used for bone grafting, since it prevents from break, enables adhesiveness of cells and assembly of extracellular matrix. Collagens from animals or human sources are implied in the construction of artificial skin in the management of burns. Also, it has properties like resistance against bacteria, fighting infection and enhance healthy granulation tissue after burns.

Collagen can retain a large amount of water, equal to 1000 times its weight, and consequently helps to maintain or restore the physiological water content of the tissues. It should also be taken into consideration that the network formed by collagen itself is able to physically "trap" elements which are fundamental for the correct homeostasis of tissues, such as growth factors, fibronectin and glycosaminoglycans.

Different types of collagens have been identified and type I collagen is the most abundant. It is important for cell adhesion and plays a role in stabilizing the growing structures: this protein performs a mechanical action favoring the anchoring and orientation of fibroblasts and the formation of new tissue.

Fibroblasts are the most abundant cells in connective tissue and are involved in the formation of the extracellular matrix and in the production of collagen. Fibroblasts are also capable of producing other components of this tissue such as elastin and hyaluronic acid. Hyaluronic acid is a biological polysaccharide (glycosaminoglycan) distributed in the extracellular matrix of most tissues, it is strongly hydrophilic and forms a viscous hydrated gel even at low concentrations. Hyaluronic acid allows the rapid diffusion of water, solutes, and molecules, guarantees tissue hydration, and keeps the environment moist, also favoring the ideal conditions for an orderly arrangement of collagen.

Description of any accessories which are intended to be used in combination with the device:

Not applicable. The device has no accessories.

Description of any other devices and products which are intended to be used in combination with the device:

The medical device has to be injected with a common CE-marked fine injection needle with a size of 30G in the deep derma.

4. Risks and warnings

Contact your healthcare professional if you believe that you are experiencing sideeffects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your healthcare professional if needed.

How potential risks have been controlled or managed

In the Risk Management Plan of COLLAGEN POWDER VIALS, STERILE, all hazardous situations related to the biocompatibility with the human body have been identified

On the basis of the risk analysis results, the adopted control measures are proven to be effective in maintaining the possible risks related to the use of the product in the levels of acceptability.

The analysis of the overall residual risk compared with the acceptability ranking defined in the Risk Management Plan is acceptable and none of the mitigation actions have introduced a new risk. Furthermore, each residual risk does not exceed the expected benefit to the patient.

It can be concluded that the overall residual risk is balanced by the benefits brought by the use of the product resulting in a favorable risk/benefit ratio.

Remaining risks and undesirable effects

The product is hypoallergenic. No side effects associated with the product have been reported. Patients should be informed of potential side effects secondary to administration of this medical device by means of injection; these might appear immediately or some time after administration. They include (but are not limited to):

- Slight stinging sensation, which disappears in a few minutes;
- Inflammatory reactions (such as redness, swelling, edema, erythema, etc.), sometimes in conjunction with itching, or pain to touch, or both. These reactions can last up to one week;
- Bruises/Hematomas;

- Hardening or nodules at the injection site;
- Coloration or discoloration of the treated area;
- Cases of necrosis of the glabellar region, abscess, granuloma, and immediate or delayed hypersensitivity after collagen injections have been described in the literature. It is therefore imperative to take these potential risks into account;
- Inflammatory reactions lasting longer than a week or other side effects must be immediately reported by patients to their practitioner, who will provide adequate treatment to eliminate such reactions.

Any other undesirable side effect associated with injection of NITHYA must be reported to the distributor and/or manufacturer.

Warnings and precautions

- Before starting the treatment, the patient should be informed of the device's indications and contraindications, as well as of its incompatibilities and possible adverse effects. As with any other intracutaneous treatment, the product may pose a risk of infection.
- Before injecting, thoroughly disinfect the area to be treated. The usual precautions for intradermal infiltrations should be observed.
- Inject slowly. Failure to comply with these precautions may lead to needle detachment and/or product leakage in the Luer lock area.
- The amount of injected product will depend on the area to be treated.
- After injection, it is important to massage the treated area to evenly spread the product. - Do not use in case of known individual hypersensitivity to the product.
- Do not inject in skin areas with active infection or inflammation.
- The product is not recommended during pregnancy and breast-feeding, although specific contraindications are not known.
- The physician's technical ability is essential for the treatment's success, therefore this medical device should only be administered by physicians who have received specific training in injectables.
- Altering the product or using it in any way that is not in accordance with the conditions of use described in this document may affect its sterility and performance, which will not be guaranteed any longer.
- Make sure that the package and the glass vial are intact before use. The product is for single use; do not reuse any remaining solution after its first opening. Quality and sterility can be guaranteed only for vials / packages sealed at the origin.
- Dispose of this product responsibly after use.
- Please check the product's expiry date and do not use it after it has expired.

KEEP THIS MEDICINE OUT OF THE SIGHT AND REACH OF CHILDREN INTERACTIONS

There are no known interactions with other substances.

Summary of any field safety corrective action, (FSCA including FSN):

- No safety findings requiring close monitoring were identified
- No FSCA has been identified

5. Summary of clinical evaluation and post-market clinical follow-up

Clinical background of the device

The medical device should be used in the correction of deep facial cutaneous sagging (chrono and photo aging signs).

When for various reasons the physiology or the mechanical characteristics of the dermis are altered, not only the dermal tissue is affected but also the overlying epidermis (to which the dermis offers mechanical and functional support), with a general impairment of the health of the skin. At a clinical and functional level, alterations in the physiology of the dermis leads to a decrease in fibroblastic activity, slowdown in collagen turnover, decrease in the level of hydration, drops in elastin levels, general loss of volume and skin atrophy. On a macroscopic level, these condition cause loss of tissue volume, thinning of the dermal layer, skin relaxation, wrinkling (particularly in the face area), excess skin in the upper and lower eyelids, prominence of the nasolabial folds, ptosis of the forehead.

The physiological skin aging process also leads to alterations of dermal physiology its mechanical and structural characteristics of the dermis, with collagen fibres becoming less stable and resistant over time and fibroblasts reducing their activity so that the turn-over between old and new collagen slows down.

Environmental factors such as exposure to UV rays, prolonged exposure to heat and pollution accelerate skin aging. Prolonged states of oxidative stress can cause structural alterations of the dermis, as free radicals can attack collagen, favouring cross-links between the fibers that become less elastic and less resistant, leading in the long term to a loss of tissue tone.

Finally, the psychological implications of the clinical conditions described above should not be underestimated. Given the direct impact on people's outward appearance, patients often begin to suffer from low self-esteem and low self-esteem.

The clinical evidence for the CE-marking

Efficacy

The manufacturer collected data on use of the medical device from one clinical study and spontaneous statements (3 clinical experience reports) by medical personnel who used the product in daily medical practice.

In total, clinical trials involved about 240 patients and the data collected on these patients confirmed the safety of injectable collagen powder.
The study by Sparavigna and collaborators (Sparavigna 2017) involved 72 healthy female subjects

aged between 40 and 65 years who were treated for correction of the signs of chrono- and photo-ageing three times with 70 mg of injectable collagen powder two weeks after each treatment.

The patients were then observed for six months. In terms of safety, the results were excellent: the injectable collagen powder was well tolerated and no systemic reactions were reported. Only a few patients reported burning sensation and bruising at the injection site, events that were resolved spontaneously within 5-10 days. In addition, doctors reported that these events could be related to the procedure for administering the product and not just the product as such. It should also be noted that of the 152 patients involved, 147 patients completed the study and 5 withdrew for personal reasons unrelated to safety aspects.

In a second study, 152 patients aged 35 to 65 years were treated every 15 days with 200 mg of injectable collagen powder for a total of 4 treatments. At the end of the observation, only 7 cases of undesirable reactions (3 cases of erythema, 2 cases of itching, 2 cases of painful perception) were found out of a total of 608 treatments (4 treatments per patient, 152 patients).

In daily medical practice, it was reported that the product tested on 20 women did not give rise to safety issues. No cases of erythema or haematomas were found 24 hours after treatment, as well as no cases of ecchymosis or haematomas; some patients complained of pain at the injection site, easily treatable with 1g of Paracetamol and lasting no longer than 48 hours.

Daily clinical experience in the use of injectable collagen powder was then collected on 40 female patients. There were no cases of erythema or haematomas after 24 hours, with the exception of the lips and surrounding areas. The pain, perceived by some patients, was well controlled with 1 g of paracetamol and totally disappeared within 48 hours. During treatment, neither cases of ecchymosis nor haematomas took place, confirming the safe use of the product.

Safety

The safety claims of the device are considered fully supported on the basis of the biocompatibility data showing not cytotoxic, mutagenic, irritating, sensitizing, toxicity and implant issues related to collagen, on the basis of the safety data retrieved from the literature and on the basis of the performed clinical study.

6. Possible diagnostic or therapeutic alternatives

When considering alternative treatments, it is recommended to contact your healthcare professional who can take into account your individual situation.

General description of therapeutic alternatives

Injectable collagen powder is designed to act where dermis and connective tissue are damaged, with reduced volume and loss of physiological characteristics. These conditions also impact the overlying skin, which tends to lose its structural characteristics and become more fragile and thinner.

There are several therapies used in clinical practice for the resolutions of the above conditions; to choose the most appropriate therapy, it is always necessary to take into consideration a number of

variables, such as the size of the area to be treated, the specific condition of the area to be treated, the patient's general health status, and the patient's medical history. Since these are also treatments for conditions that by their very nature also have aesthetic implications, it is important that the patient is also properly informed of the aesthetic effect that the treatment may or may not have.

Among the most common therapies for correction the deep facial cutaneous sagging (chrono and photo aging signs) there are "dermal fillers." These are products designed to be injected directly into the dermis, where they help restore tissue physiology.
Conceptually, these products can act in two ways: "passively," i.e., acting as simple filler agents, or "actively," i.e., promoting and supporting the recovery of physiological functions of the tissue.
Passive fillers therefore have only a structural role, restoring tissue volume to optimal levels. In this case, there are no biorestoration effects and the effect is mainly cosmetic: the tissue regains texture and volume but does not recover its normal physiology. Usually these products are not biodegradable or poorly biodegradable and are therefore presented as permanent treatments. Common passive dermal fillers are silicone and polymethylmethacrylate.
Other fillers, on the other hand, have an active role, that is, they do not just restore tissue volume, but their main action is to stimulate tissue activity so that normal tissue physiology is restored. Most of these products biodegrade over time. Euroresearch's injectable collagen powder falls into this category of products; other common products include hyaluronic acid fillers, calcium hydroxyapatite, and poly-lactic acid.
Peeling is another widely used therapy. Peeling is based on the principle that damage to the epidermis and dermis itself can naturally stimulate fibroblastic activity. In fact, it is known that the inflammatory response following damage stimulates the deposition of new collagen; consequently, controlled damage leads to the production of new collagen and tissue revitalization. Over the years, peeling has been performed by various methods, using either chemical agents (e.g., phenol, trichloroacetic acid) or physical agents (e.g., dermabrasion, microdermabrasion, or laser) or combining chemical and physical agents. The main risk of this technique is related to the fact that the damage done to the tissue is too incisive and that in the long run there may be problems, primarily excessive thinning of the skin. In addition, excessive damage could stimulate more fibrosis at the expense of new collagen deposition with repercussions on the effectiveness of the treatment.
Lifting is another widely used therapy. These surgical treatments have been studied to correct some specific defects of face, focusing only on the aesthetic aspect of the loss of functionality of the dermis and epidermis. These treatments therefore aim to restore the "youthful" appearances of the tissue, without promoting the restoration of the tissues themselves.
They present all the potential risks associated with surgical operations (bleeding, infections, long recovery times).
Another alternative is represented by Botulinum.
Botulinum has an effect on wrinkles and facial skin as it acts on the underlying muscle contractions. Injection of botulinum toxin into the muscles under facial wrinkles causes relaxation of those

muscles, resulting in the smoothing of the overlying skin. Several commercial products are available on the market, classified as drug product. The safety of this treatments is well known however adverse events can occur. Side effects include headaches, flu-like symptoms, and allergic reactions; furthermore in case the toxin is injected into the wrong muscle group or with time spread from the injection site, it may cause temporary paralysis of unintended muscles causing partial facial paralysis or muscle weakness. These symptoms may last for weeks. This is the reason why in 2009, the US FDA announced that boxed warnings would be added to available botulinum toxin products, warning of their ability to spread from the injection site.

Botulinum is generally administered in outpatients care and no specific recovery times are required after the treatment. The effect is not permanent, and treatments should be regularly repeated to prolong the effect.

However, the treatment is limited to the external and aesthetic aspects only, without treating the primary causes of the situation. This means that it is not possible to reach a recovery of the physiological properties of the tissue and there is no direct action at dermal level.

Therefore, the medical device falls into a framework of established medical treatments.

7. Suggested training for users

The product must be administered by healthcare professionals only. The physician's technical ability is essential for the treatment's success, therefore this medical device should only be administered by physicians who have received specific training in injectables