novuma®

Application Protocol

BURGEON

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NOVUMA UYGULAMA PROTOKOLÜ

INTRODUCTION

This protocol has been created to provide information to the physician who will apply NOVUMA® injectable implant by bringing together detailed information about the process of use. This protocol is based on the studies in the scientific literature and was developed by Medical Department of Burgeon Biyoteknoloji and San. Tic. AŞ.

This protocol has been prepared to guide physicians who are authorized to apply NOVUMA® . The information contained in the protocol is based on safe application procedures and aims to answer questions that physicians may have about the application.

The protocol consists of 3 main sections; Preparation for Application, Application Process and Post-Application Process. The information in this protocol has been prepared only for the practitioner physician to easily access the information in the current literature on all steps in the application of the NOVUMA® injectable implant to patients. The information contained in the protocol may become outdated due to changes in the current scientific literature and may not reflect the latest legal developments in force. For this reason, it will be updated every year in September and will be published on https://www.burgeon.me/. Please make sure that the protocol you are using is the most recent version published.
The information in this protocol is intended to guide physicians on applications and Burgeon Biyoteknoloji ve San. Tic. AŞ. cannot be held responsible.

We would like to thank Prof. Dr. Tolga Reşat Aydos for his support in the scientific content and editorial editing of the Pre-Application and Post-Application sections, and Op. Dr. Ercan Cihandide for his support in the Application and Post-Application sections.

1-PRE-APPLICATION

This section contains general information about NOVUMA® before the NOVUMA® injectable implant purchased as a final product is applied to patients, information in the literature about the active substance, NOVUMA® application indications and clinical features, anatomy information about the body area to be applied, the general approach in case of adverse effects and the points to be considered when applying NOVUMA®.

1.1-General Information about Skin and Calcium Hydroxylapatite (CaHA)

The skin is the heaviest organ of the entire body and accounts for 16% of total body weight. It forms a protective physical barrier between the body and the environment, prevents water loss, reduces the entry of chemicals into the body and provides protection against pathogenic microorganisms. It receives sensations of touch, vibration, pressure, temperature, heat and itching through sensory and autonomic nerves and receptors. Melanin, a pigment produced and deposited in epidermis cells, creates a protective effect against UV rays of the sun. Because the skin is elastic, it can expand to cover large areas when accompanied by swelling, such as edema and pregnancy. [1]

The epidermis, the outermost layer of the skin, consists of 5 layers.

Stratum Germinatum (Basal Layer): a layer of cells on the basement membrane at the dermis-epidermis junction. It is responsible for the continuous renewal of epidermal cells. It renews the epidermis every 15-30 days depending on its location in our body and environmental factors.

Stratum Spinozum: Consists of cells with cytoplasmic extensions filled with bundles of keratin filaments. These filament bundles come together to form numerous small cellular projections and terminate in desmosomes located at the ends of these spiny projections. Stratum Spinozum and Stratum Germinatum together form the Malpighi layer. Only the Malpighi layer contains epidermal stem cells.

Stratum Granulosum: Consists of a layer of cells filled with keratohyaline granules. These granules are released from the cell membrane to form a fatty layer that acts as a barrier to the penetration of foreign substances.

Stratum Lucidium: A translucent thin layer of highly flattened cells, more prominent in thick skin.

Stratum Corneum: It consists of a layer of nucleus-free cells filled with a filamentous scleroprotein called light birefringent keratin. After keratinization, the cells here lose their stoplasmic content.

The dermis is the connective tissue that supports the epidermis and connects it to the subcutaneous tissue. The thickness of the dermis varies according to its location and reaches its maximum thickness in the dorsal region. The dermis contains two layers with barely distinguishable borders; the outermost papillary layer and the deeper reticular layer. The papillary layer is composed of loose connective tissue and contains fibroblasts and other connective tissue cells, most commonly macrophages and mast cells. The reticular layer is thicker and consists of irregular connective tissue, mainly Type I collagen. This layer contains glycosaminoglycans such as dermatan sulfate and hyalineuric acid. The dermis has a rich network of blood and lymph vessels. In addition to these structures, the dermis contains hair follicles and epidermal structures such as sweat and sebaceous glands. [1,2]

Table 1: The Most Common Types of Collagens in the Body

Collagen Type	Molecular Formula	Protein Structure	Tissue Distribution
1	$[\alpha1(I)]_2\alpha_2$	Fibril	Skin, Tendon, Bone
2	$[\alpha1(II)]_3$	Fibril	Cartilage, Cornea
3	$[\alpha1(III)]_3$	Fibril	Skin, Uterus, Vascular Structures
4	$[\alpha1(IV)]_3$	Network	Basal lamina, renal glomerulus
7	$[\alpha1(VII)]_3$	Short Fibril	Basal Lamina

Collagens, which constitute up to 25% of total mammalian proteins, provide a striking example of the diverse structure-function relationship that characterizes the fibrous proteins of vertebrates. Skin collagen forms loosely knotted, flexible fibers. Type 1 collagen is the major collagen in the skin, accounting for 80-90%.

It is synthesized mostly from fibroblasts of mesenchymal origin that reside in the dermis. Fibroblasts also synthesize elastins and Glycosaminglycans (GAGs) such as hyaluronic acid and dermatan sulfate, which give the skin elasticity. Mechanical tension, biochemical stimuli and signaling pathways in the extracellular matrix of the skin are stimulatory for fibroblasts and are effective in their activation and proliferation. With the activation of fibroblasts, collagen, elastin and GAG production increases.[3] Collagens are long-lived proteins modified by glycosylation. With advancing age, glycosylation increases and leads to a decrease in structurally active collagen. [1]

The color of the skin is determined by factors such as the content of melanin pigment and carotene, the amount and content of blood vessels in the dermis.[4] Melanin is synthesized by melanocytes in the epidermis. There are 2 types of melanin: red/yellow pheomelanin and brown/black eumelanin. Most melanin pigment is found in melanosomes between keratinocytes. While the number of melanosomes is similar in many people, their structure, size and content vary in individuals. It is also observed that graying of hair is caused by a decrease in melanin in melanosome content. Melanin is a pigment whose synthesis increases to protect the body from radiation caused by UV light. The density of melanocytes in the skin is related to environmental factors (most importantly UV sunlight) and mediators secreted by fibroblasts and keratinocytes. [5]

The subcutaneous tissue layer is a loose connective tissue that loosely connects the skin to the neighboring organs underneath and allows it to slide over them and is called hypodermis. The hypodermis contains fat cells, the number of which varies depending on the region and the size depending on the nutritional status of the person. This layer is also called the superficial fascia and in areas where it is thick enough it is called the panniculus adiposus. [4]

The skin is an important component of the perception of beauty and is therefore the focus of many surgical and non-surgical interventions. Wrinkles, loss of elasticity and pigmentation changes in the skin due to the chronic effects of age and sunlight cause patients to resort to cosmetic procedures to improve their appearance. [6]

Calcium hydroxylapatite (CaHA) ($Ca_{10}(PO_4)_6(OH)_2$) is a synthetic biomaterial that has been used in orthopedics, neurosurgery, dentistry, otolaryngology and ophthalmology for over two decades. CaHA is the main mineral component in bones and teeth. CaHA, which is highly biocompatible, increases the synthesis of type I and III collagen, elastin and proteoglycans in the injected area and provides the transformation of connective tissue into de novo formation. This transformation gives the skin a firmer, brighter, more elastic, hydrated and younger appearance with fewer wrinkles.[7]

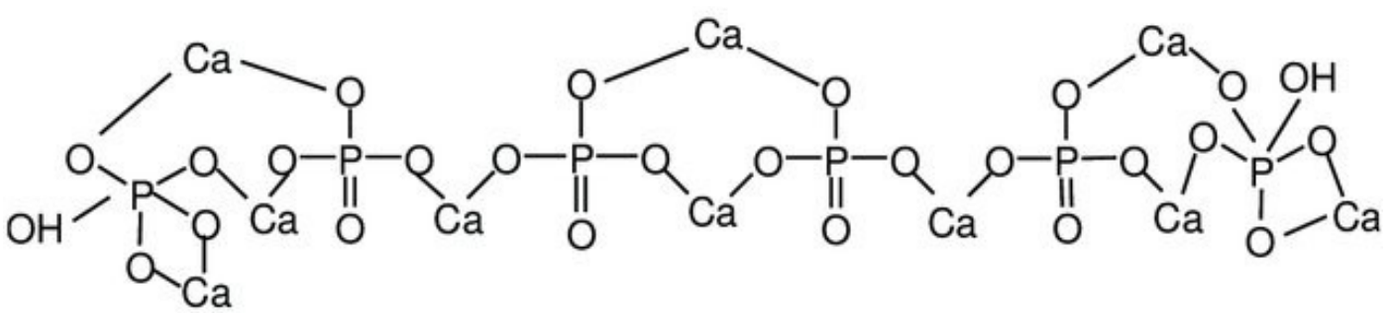


Figure 1: CaHA biochemical formula

CaHA fillers are classified as dermal fillers with medium duration of action. When used undiluted, CaHA has a high viscosity and elastic structure and is suitable for deep applications. It is a very suitable liquid implant to support the structures on the supraperiosteal surfaces. CaHA is a widely used dermal filler with good results and high patient satisfaction scores with its immediate effect. Scientific studies also show that CaHA has a generally safe application profile. [8]

Reducing the signs of aging in the lower jaw and cheek area plays a key role in facial reconstruction. Atrophy of the fat tissue in the mandibular region leads to sagging skin in the lower jaw. In the application area, CaHA microspheres act like newly formed collagen, stimulating fibroblasts and increasing collagen synthesis while preventing calcification and integration with bone.[9]

In studies with CaHA, it is seen that the most prominent benefit is in nasolabial region applications, followed by mandibular applications. Successful results are also seen in studies in which lidocaine or hyaluronic acid applications were performed with CaHA. With the increase in facial CaHA applications, the number of facial chin lift operations decreased by approximately 17% between 2015-2019 worldwide.[9]
According to ISAPS 2022 data, the number of hyaluronic acid applications decreased in 2022 compared to 2021, while the number and rate of CaHA applications increased (Table 2).

Table 2: ISAPS 2022 - Number of applications of non-surgical procedures by year

TOTAL NON- SURGICAL PROCEDURES	2022	2021	2018	Percentage Change 2022 vs.2021	Percentage Change 2022 vs.2018	
Botulinum Toxin	9,221,419	7,312,616	6,097,516	26,1%	51,2%	INJECTABLES
Calcium Hydroxylapatite	350,716	290,095	129,038	20,9%	171,8%	
Hyaluronic Acid	4,312,037	5,279,344	3,729,833	-18,3%	15,6%	
TOTAL INJECTABLES PROCEDURE	**13,884,172**	**12,882,055**	**9,956,387**	**7,8%**	**36,4%**	

Among different dermal fillers, CaHA is unique in that it functions as a scaffold for regeneration. It is a very suitable liquid implant, especially for supporting structures located on the supraperiosteal surfaces. According to global consensus recommendations, CaHA formulations are considered dilute when prepared as a 1:1 dilution and hyperdilute when prepared as a 1:2 dilution. CaHA microspheres can stimulate neocollagenesis and elastogenesis even when diluted at a ratio of 1:6.[10] When CaHA is diluted at a ratio of 1:1, the volumizing effect continues, but when it is diluted more, the volumizing effect decreases, but the fibroblast stimulating effect does not decrease. [8] In the study conducted by Botsali et al., it was observed that fibroblast stimulation and collagen production were higher than in the control group even when the stimulation with NOVUMA was diluted at a ratio of 1:19.[11] CaHA can be used to improve skin quality on the face, arms, hands, neck, décolleté, upper arm, abdomen, gluteal region and thighs and to treat striae or cellulite. In the choice of treatment, the practicing physician plays a major role in deciding whether the reason for the application to the patient is due to volume loss, lipodystrophy or decreased skin quality. For example, although CaHA filler applied in the cheek area shows volume replacement and lifting effect, it may not have the same effect in the lower jaw due to fat tissue atrophy. In general, diluted CaHA was not found to be suitable for application in the abdomen, thighs and upper arm areas with excess adipose tissue and lipodystrophy. It is important that the patient is close to the ideal weight, especially in the abdomen and thighs.[12] Some patients may expect to see the immediate volume gain effect of fillers in hyperdiluted CaHA applications. Patients should be informed that the volume gain effect will start in weeks 4-6. Patients should be informed that the effect of volume gain will start in weeks 4-6.[12] In order to achieve the optimal effect, some experts state that it is necessary to apply 2 or 3 times.

Since the outcome of the treatment depends on the collagen production capacity of the patient, this should be taken into consideration especially in applications to elderly patients. In the study by Lorenc et al., it was reported that patients requested reapplication one year after the use of hyperdiluted CaHA.[12] Hyperdiluted CaHA should almost always be applied just below the dermis in the dermal-subdermal plane.

1.2-Physiological Changes with Aging

Soft tissues start to deteriorate with aging due to many factors such as genetics, hormonal changes and environmental factors. In some people, deep soft tissues are well preserved and superficial problems occur, while in others, structural deterioration is seen in deep tissues and the skin loses its elasticity while superficial tissues remain young. Genetic influences are more likely to have an impact on conditions related to the basic soft tissue structure and morphology of the individual.

In cumulative effects, histologic epidermal thinning, changes in keratinocyte morphology and a decrease in the number of Langerhans cells and melanocytes have been shown. Environmental factors include dehydration, malnutrition, exposure to extreme temperatures, trauma, exposure to strong ultraviolet rays and smoking. Environmental factors show their effects as structural disorders and dysplasias in the dermal and epidermal structures of the skin.

Hormones play an important role in aging and show individual and gender-dependent changes. Changes in the skin are known to occur in women with decreasing estrogen levels and some can be reversed with hormone replacement therapies. Studies in postmenopausal women have shown that women with low estrogen levels have dry skin, atrophies, wrinkles, decreased skin elasticity, delayed and reduced healing.

Much fewer studies have been conducted on the effects of hormones on men with aging, and the effect is thought to be of similar importance. Pregnancy-related stretch marks (striae gravidarum) affect 90% of women and are caused by the viscoelastic tension force of the skin. During pregnancy, hormones reduce the bonds between collagen fibrils and increase the appearance of stretch marks. Stretch marks around the belly are very common and it is almost impossible for the skin to return to its original elasticity on its own. [13]

Conditions that increase in frequency with aging[24]

- Horizontal skin wrinkles on the forehead and vertical wrinkles on the glabella
- Sagging in the lateral parts of the eyebrows
- Sagging upper eyelid skin
- Reduced lower eyelid laxity and formation of wrinkles
- Lower eyelid bags
- Deepening of nasolabial lines
- Sagging in the malar region
- Reduced skin elasticity
- Plastismal bands become visible and increase in prominence with facial expressions
- Wrinkles around the mouth
- Deepening of the labiomental lines

After the age of 30, epidermal melanocytes decrease by 10-20% in each decade.[5] As the age progresses, the ratio of Type I collagen (80%) and Type III collagen (15%) in the skin decreases by 1% to 1.5% each year. As the collagen level decreases, the collagen structure becomes more fragile and the structural support of the skin weakens. This causes the skin to lose volume, lose firmness and become thinner and wrinkled. The decrease in collagen production also occurs simultaneously with skin hydration and nutrition problems due to loss of hyaluronic acid.

With age, collagen fibers thicken and collagen synthesis decreases. Elastic fibers steadily increase in number and thickness. Thus, the elastin content of human skin reaches five times that of the fetus in adulthood. In old age, the large number of cross-links in collagen fibers, loss of elastic fibers and degeneration of fibers due to excessive sunlight (solar elastosis) lead to thinner skin, loss of elasticity and wrinkles.

For this reason, many anti-aging applications try to show their effect through fibroblast stimulation. [13]

"Severity of Wrinkles Rating Scale (SWRS)" is used to guide clinicians for facial wrinkles. This 5-stage scale aims to create a common language of expression for facial wrinkles and to ensure standardization.[14]

Grade I: Describes when the nasolabial fold is not visible. Skin lines show continuity. There is no need for implant application.
Grade II: Describes a mildly formed nasolabial fold. It is subtle and visible with minor facial movements and manipulation. Implants are expected to provide moderate improvement in appearance.
Grade III: Describes a moderately deep nasolabial fold that is visible even when the face is not tense. Near perfect correction is expected with injectable implants.
Grade IV: Describes a long and deep nasolabial fold. A nasolabial fold less than 2 mm deep can be seen when the mimic muscles are stretched. Significant improvement is expected with injectable implants.
Grade V: describes a very deep and long nasolabial fold. V-shaped visible folds between 2-4 mm are not expected to improve satisfactorily with injectable implants.

1.3-GENERAL INFORMATION ABOUT NOVUMA

NOVUMA® is a biocompatible, sterile, ready-to-inject injectable implant containing Calcium Hydroxylapatite and carboxymethyl cellulose as excipients manufactured by Burgeon Biyoteknoloji, Ankara, Türkiye. The active ingredient accounts for 60% of the mass content, with excipients accounting for the remaining 40%.

When you open 1 NOVUMA® injectable implant box, it contains 1.5cc ready-to-use NOVUMA® injector, 1 user manual, 3 patient labels, 1 dilution card. At the end of the Quality Controls performed at the end of the production process, a Quality Control label is affixed on both sides of the box. Considering the possibility of counterfeit or faulty products, do not apply products with missing Quality Control labels and return them to the distributor you have obtained.
The semi-solid nature of the NOVUMA® injectable implant is created by suspending calcium hydroxylapatite in a gel carrier consisting mainly of water (sterile water for injection USP) and glycerin (USP). The NOVUMA®injectable implant is classified as a Class III Medical Device according to Annex IX of the Medical Devices Directive. The NOVUMA® injectable implant contains CaHA crystals with a particle size between 25-45 microns and can be injected with a needle of 25 gauge outer diameter and 27 gauge inner diameter or larger with a standard Luer Lock adapter.

The effectiveness of NOVUMA® , which has the ability to increase both the number and the amount of collagen produced by fibroblasts, whose number and activity decreases with aging, has been demonstrated by clinical research. It creates a strong biostimulant effect on the underlying cause of the connective tissue that decreases with aging, not artificially. Used safely since 2020, NOVUMA® is distinguished from its competitors due to its high user satisfaction and no reported systemic or serious side effects.

CaHA in NOVUMA® is a molecule with very high bioavailability, has been used safely for many years in different indications and has been the subject of numerous scientific studies. Instead of physically filling the application area, it provides a more natural result with its biostimulator effect that leads to increase the amount of reduced collagen, which is the main source of the problem. It has a longer duration of action compared to hyaluronic acid fillers, which reduces the frequency of application to the patient.[9,12,13] With the increased amount of collagen and skin quality, it provides a younger appearance by creating a lifting effect in the application area, increasing skin brightness and reducing sagging in the skin.

novuma®

CaHA Dermal Filler

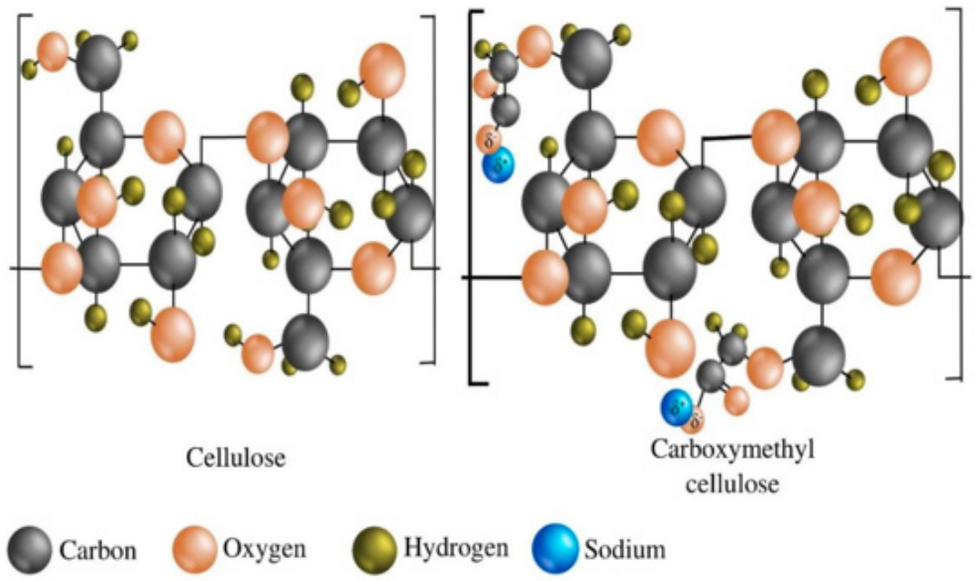


Figure 2: Molecular Structure of Cellulose and Carboxymethyl Cellulose [42-15]

Carboxymethyl cellulose (CMC) in NOVUMA is an anionic, water-soluble form of cellulose. Carboxymethyl cellulose is a linear polysaccharide. Its effect is instantly visible and it is the ingredient that provides the filling and lifting effect on the face in the short term. Carboxymethyl cellulose dissolves completely within an average of 12 weeks, loses its effect and is completely absorbed by macrophages in the connective tissue.[15] CaHA breaks down into calcium and phosphate over time and is metabolized by macrophages through phagocytosis. Due to this structure, it is considered completely biodegradable. The effect of fillings containing CaHA is usually between 12-18 months and this effect may end sooner when used diluted.[42]

Due to the CMC and CaHA in NOVUMA®content, the lifting and filling effect is provided by two different mechanisms. CMC effect starts to be seen immediately and disappears between 8-12 weeks. The biostimulatory effect of CaHA starts to be seen actively at 8-12 weeks. Thus, the increase in skin quality, lifting and filling effect is seen from the moment of application until the 12th-24th months. Diluted application may shorten its biological life and cause the effect to end more quickly.[42]

In dermal fillers containing CaHA, the microsphere size of CaHA crystals should be between 25-45 microns. Smaller microspheres are phagocytized by macrophages and larger microspheres may cause nodule and granuloma formation. The smooth surface of the microsphere structure protects it from phagocytosis and prevents the development of allergic reactions. When NOVUMA® and other CaHA-containing implants are compared under electron microscope, the differences in Figure 3 can be seen. It can be seen that NOVUMA® microspheres retain their perfect spherical structure and have a surface that is almost completely smooth compared to other implants.

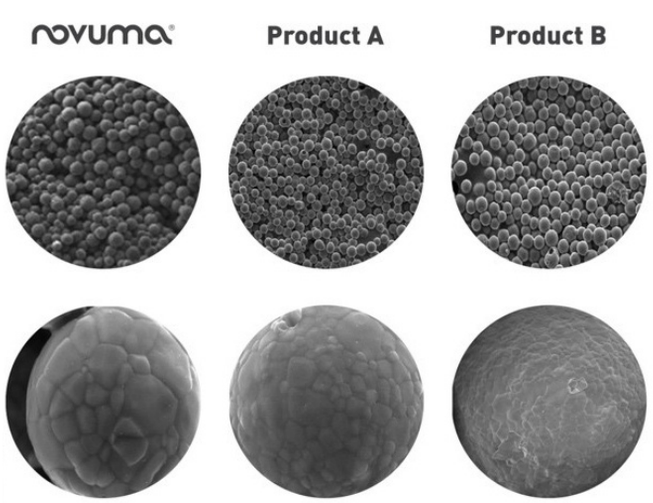


Figure 3: Electron microscopic images of dermal implants containing CaHA

NOVUMA® requires less extrusion force for application compared to other implants containing CaHA. This provides both ease of application and less fatigue in the hand muscles during the day for the practitioners. In this way, it provides both safer and more applications.

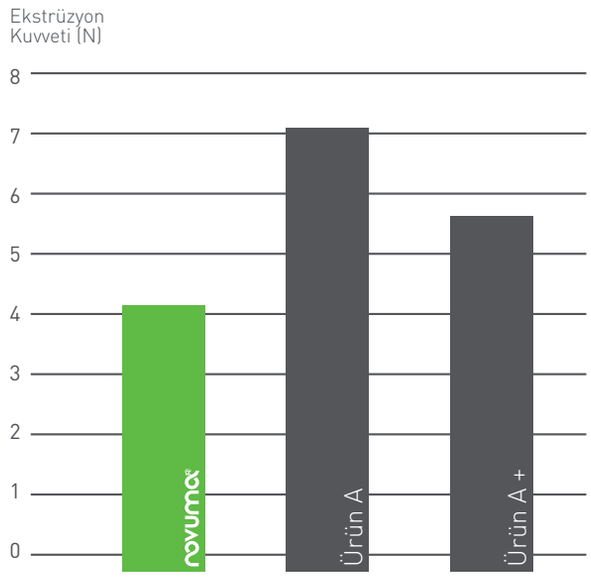


Figure 4: Extrusion forces comparison between NOVUMA® and CaHA-containing products on the market for the same indication

NOVUMA® has the highest density of Calcium Hydroxylapatite crystals compared to other implants containing CaHA in thermogravimetric studies. This allows NOVUMA®, to produce higher efficacy in the same volume.

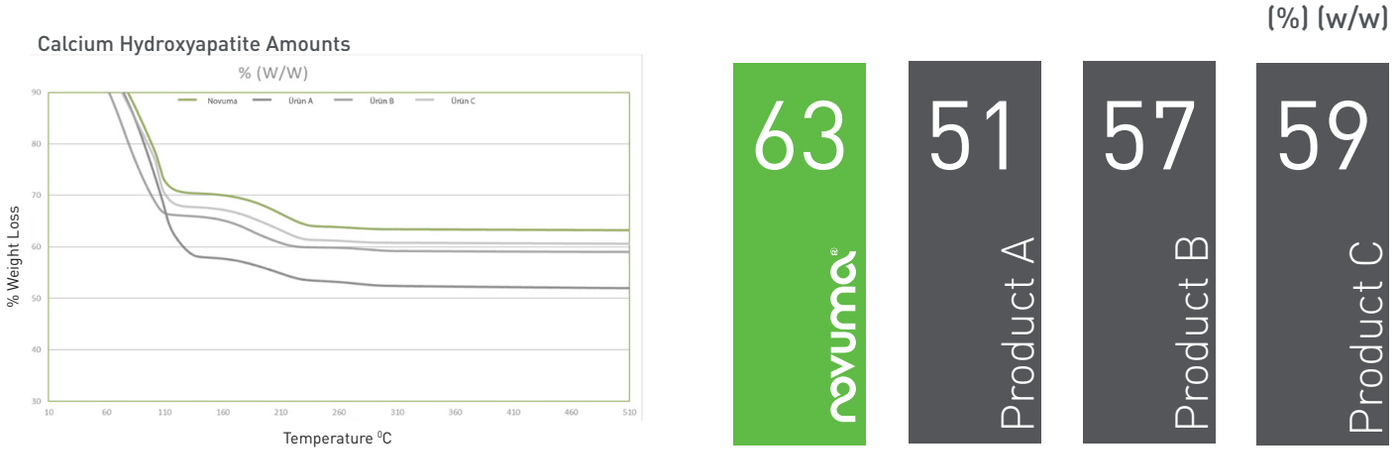


Figure 5: NOVUMA® thermogravimetric comparison of CaHA-containing products used for the same indication in the market

1.4- Clinical Features

NOVUMA® injectable implant is applied as a subdermal implantation for the correction of skin wrinkles, folds, sagging skin and for the elimination of signs of facial fat loss caused by decreased elasticity and mechanical tension resistance of the skin due to deterioration of the connective tissue structure such as aging, sun rays, stress, smoking. The connective tissue growth replacing the gel carrier is normally completed within a few months due to the good biocompatibility of the microspheres. Over time, the defective area is filled with autologous connective tissue. Due to their unique physical properties, the total bioavailability of hydroxyl apatite microspheres is predictable, controllable and adjustable.

NOVUMA® can be used in the cheekbone, nasolabial folds, chin, jawline, jaw fold, lower cheek, bridge of the nose, oral commissures, laugh lines in the face area.[11,16] It has been shown in various scientific studies that other implants containing CaHA are also applied in the hands, neck, décolleté, hips, knees, skin cracks due to tension and positive results are obtained.[17,18,19,20]
NOVUMA® is contraindicated and should not be used in the following cases:

-If the patient has an allergy to any of the ingredients,
-If the patient has a history of anaphylactic shock,
-If the patient has had keloid formation before or has a known predisposition,
-If there is a risk of failure to maintain hemostasis in hemorrhages that may occur due to injection in patients with known coagulation disorders,
-The patient has an acute and/or chronic infection at the site of treatment,
-If the patient has a previous herpetic infection,

-If the patient has systemic steroid use as it may impair connective tissue regeneration,
-The patient has foreign bodies such as fluid, silicone or other particulate material in the application area,
-Patients with known connective tissue disease,
-The patient has a systemic disease that delays wound healing or a disease that would cause tissue degradation on the implant.

1.5-Overdose and Treatment

There is no overdose reported in the literature for NOVUMA® and other CaHA-containing implants. Considering that NOVUMA® shows its effect locally and has no systemic side effects reported to date, it is of great importance to comply with safe subcutaneous and intradermal application limits. Since there is no antidote for NOVUMA® that will quickly reverse its effect, it is recommended not to apply higher doses than the recommended doses in the application area.
In the light of the available literature, 1.5 cc is considered to be the optimum application volume at one application site for subcutaneous injection, while pain, pain and adverse effects at the injection site and backward flow of the solution have been reported to occur in applications with volumes higher than 2.5 cc. [21] However, no comparative scientific study has been conducted to demonstrate this situation. For NOVUMA® and other CaHA-containing dermal fillers, no study on the maximum application dose at an application site has been published. NOVUMA® is prepared as a 1.5 cc ready-to-use syringe and is suitable for use in one application site (Detailed information on application sites and doses is given in Section 2.9 Application Techniques).If more volume is administered to an area than necessary, it is appropriate to distribute and spread the injection content with vigorous massage of the application area.

1.6 Adverse Effects

No systemic adverse effects have been reported for NOVUMA® and other CaHA-containing dermal fillers published to date. Depending on the content of NOVUMA® and the application technique, some undesirable local effects may occur. The side effects that may occur due to intradermal injections and the application of NOVUMA® are described below. In case of an undesirable effect other than those listed below, you can notify us at feedback@burgeon.me

Contextual Adverse Effects

•**Allergic Reactions:** Although no Type I hypersensitivity reactions have been reported to date, allergic reactions with systemic or local symptoms may develop against the molecules contained in NOVUMA® .

Undesirable Effects Depending on the Mode of Application

Edema: The development of edema in intradermal applications is considered normal due to tissue trauma due to the application. In case of edema exceeding 48 hours, pathologic conditions should be considered.

Pain: It is considered normal for the patient to feel pain during the application. In cases of pain lasting longer than 2 hours, pathological conditions should be considered.

Erythema: It is considered normal to develop erythema due to pressure during application and injection. In case of erythema exceeding 48 hours, pathological conditions should be considered.

Ecchymosis: Ecchymosis may develop due to damaged capillaries during application. Ecchymoses are expected to dissipate completely and pathologic conditions should be evaluated in longer lasting cases.

Hemorrhage: Hemorrhages may occur at the injection site due to damaged vascular structures during administration. Injection-related hemorrhages may occur if the patient is taking medications that prolong bleeding such as aspirin or warfarin or has an underlying systemic disease.

Hematoma: It may occur when vascular structures in subcutaneous tissues are damaged and blood coming out of the vein accumulates under the skin.

Paresthesia: Numbness may be felt in the application area due to intradermal applications or if applied with a local anesthetic drug during application. Although it varies according to the type of local anesthetic drug, pathological conditions should be evaluated in cases exceeding 4-6 hours.

Necrosis: It may occur as a result of insufficient nutrition of tissues due to intravascular administration or external compression of the vessel wall. It is one of the conditions requiring urgent intervention.

Paralysis: It can be seen after applications to the wrong application site. It is one of the situations requiring urgent intervention.

Scarring: Scarring may develop as a result of application to inflamed or infective tissues, the presence of systemic disease-causing problems in wound healing or arterial occlusion. Rapid intervention and follow-up are required.

Granuloma: Although no granuloma has been reported to date, the risk of granuloma formation due to foreign body reaction is very low for all intradermal injections.

Papule and Nodule Development: It may develop as a result of application to superficial tissue.

Arterial Occlusion: It may develop if the application is performed intravascularly. It is important to recognize it in the early stages as it can lead to coagulation necrosis of tissues.

Infection: It may occur due to lack of adequate aseptic precautions, use of non-sterile equipment or transfer of the source of infection from existing infective tissues. The patient's history of previous surgical intervention should be taken carefully because of the possibility

of displacement or anatomical variations of arteries and veins and weakened vessel walls. Because these anatomical variations may lead to an increased risk of ischemia, necrosis and vascular embolism. [25]

1.7-Warnings

To minimize the risk of possible complications, NOVUMA® should only be applied by experienced specialists. Applicators should be fully informed about the product and the product-related educational materials.

Avoid the use of products that are not stored under appropriate conditions or that have expired.
Boxes that do not bear the "Quality checked" label on both sides of the box should not be used on patients and should be returned to the distributor.

There are no studies on the use of CaHA-containing fillers or NOVUMA® ready-to-use implant in humans during pregnancy. Since there is no scientific data on the safety of use during pregnancy and lactation, it is not recommended for use in pregnant and breastfeeding patients.

NOVUMA® ready-to-use implant has no systemic side effects reported to date, but there are no scientific studies on NOVUMA® or CaHA-containing fillers on the ability to drive and operate machinery.

NOVUMA® does not contain any compound that would reverse or immediately dissolve the effect of the ready-to-use implant. NOVUMA® is not suitable for intravascular administration due to the risk of occlusion. Therefore, the anatomy of the application site should be well known by the practicing physician.

NOVUMA® is packaged for single patient use in one treatment session. Reuse may result in an increased risk of infection and reduced efficacy. The NOVUMA® syringe is not suitable for re-sterilization and use.

Excessive force on the injection port of the product should be avoided due to the risk of freezing. Since NOVUMA® containing CaHA can be applied with less extrusion force than other implants, consider this feature if you are using NOVUMA® for the first time.

Scar tissue or damaged tissue may not properly accept the NOVUMA® injectable implant. Therefore, application in areas of active inflammation should be avoided.

The injection procedure of the NOVUMA® injectable implant has a small risk of infection and/or bleeding like other similar injection procedures. The patient may experience mild discomfort during and after the procedure. Patients taking medications that prolong bleeding, such as acetyl salicylic acid or warfarin, may experience increased bruising or bleeding at the injection site, as with any injection.

General precautions for percutaneous injection procedures should be followed at the site of administration to prevent infection at the site of administration. The injection site should be cleaned with an appropriate antiseptic. Injecting the NOVUMA® injectable implant into patients with a history of herpetic rash may result in reactivation of Herpes zoster.

Considering the risk of rupture in the application area, multiple injections to the same area and excessive force during the injection process should be avoided. In order to prevent needle breakage, bent needles should not be tried to be straightened. If the needle is bent, the application should be performed by replacing it with a new needle.

If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with the NOVUMA® injectable implant, the risk of a possible inflammatory reaction at the implant site should be considered and at least 4 weeks should be allowed between these procedures.

CaHA is a radiopaque substance and it will be seen clearly separated from the surrounding tissues on Computed Tomography imaging. The physician who performs and interprets imaging must be informed in order not to consider it as a lesion.

Since there may be a risk of contact with the patient's body fluids during application, necessary personal protective measures must be taken. Used products should be disposed of as detailed in Section 3.6.

1.8-Shelf Life and Storage Rules

The expiration date is 2 years from the date of manufacture. Do not use expired product. The expiration date is printed on the product label.

The packaged NOVUMA® injectable implant should be stored in its box at a controlled room temperature between 15°C and 32°C (59°F and 90°F). It should not be placed in the refrigerator as cold temperatures may cause the injector to freeze or dry out.

NOVUMA® should be stored in an area out of direct sunlight as storing it in direct sunlight may disrupt its structure.
The injector of the NOVUMA® injectable implant is leak-proof and not affected by moisture.
Since NOVUMA® injectable implant content is sterile, actions that will disrupt its sterility should be avoided. It should be kept in its packaging until the time of application.

2-Application

In this section, the points to be considered during the application of NOVUMA® injectable implant to the patient who has been decided to be implanted are emphasized.
In this section, the anatomy of the application areas, preparation of the product, preparation of the patient for the procedure, different techniques related to the application to be performed and the advantages of the techniques over each other will be explained. A very good knowledge of the anatomical structures in the

area of application will both increase the success of the procedure and reduce the risk of complications. Information about the correct preparation and dilution of the product will be presented in order to avoid any obstacles to the application of the product and to achieve better results and fewer complications with correct applications.

2.1-Facial Anatomy

The body connects people through the senses. The face is like a space where personal meaning is embodied and at the same time where past experiences are stored. As an organ of expression, the face has a purely theoretical nature. It does not act like hands, feet or the body as a whole, it never supports people's inner or practical behavior, it only tells others about it.[22] The face is the special name of the region that extends from the hairline to the mental projection on the front of the head and is bounded laterally by the preauricular regions.

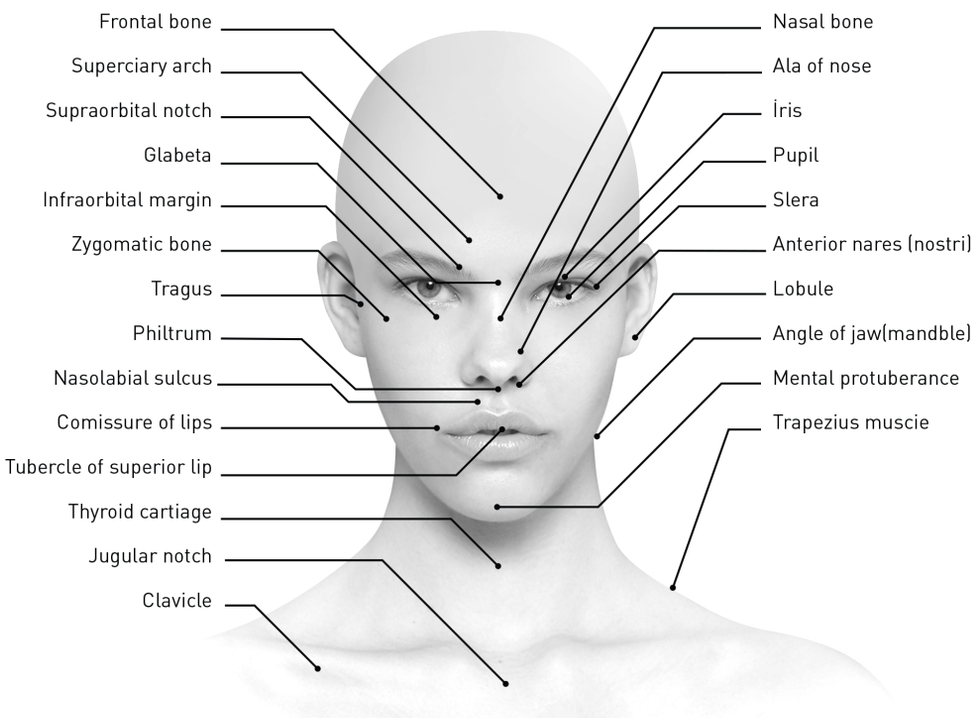


Figure 6: Important anatomical landmarks on the face

The bones that make up the face are the mandible, maxillary, zygomatic, nasal, ethmoid, vomer and frontal bones. This bone structure is covered with many muscles. There are deep and superficial fat pads on the musculoaponeurotic structures formed by the muscle structures. The face has no deep fascia, only superficial fascia. Superficial fascia has 2 layers. Mimic muscles are located between these 2 layers. Atrophy of these fat pads is observed with advancing age or due to some diseases such as HIV and is an important cause of wrinkles and sagging on the face.

The face is a complex area to treat, with a well blood supply, many arterial structures and a nerve supply with numerous innervations. The blood supply to the face is provided by branches arising from the a. carotica communis. The a. facialis, a. maxillaris, a. transversalis facialis and a. superficialis temporalis are branches of the a. carotica externa, while the a. ophtalmica, which provides blood supply especially to the forehead, is a branch of the a. carotica interna.[27]

The a. carotica interna enters the head from the canalis carotica and makes an anteromedial turn towards the cavernous sinus, where the a. ophtalmica gives its branches. A. ophtalmica gives supraorbital and supratrochlear branches in the orbit. These branches travel in the deep layers of the frontal muscle and provide blood supply to the medial orbit and forehead region.

A. carotica externa gives two main branches after turning the mandibular corner. The first is the a. temporalis superficialis. The artery runs along the lateral margin, first subdermal but then descends into the deep layers of the facial muscles and anastomoses to the a. supraorbitalis and a. supratrochlearis. In the lateral part of the face, it supplies the n. facialis, facial muscles and skin, and with branches higher up it supplies the temporal region, forehead and lateral skull. The second branch is the a. maxillaris interna. It runs behind the mandible, gives off the inferior alveolar branch and then supplies the lower lip, gingiva, oral cavity and chin, terminating in the a. mentalis. Another important branch is the a. infraorbitalis. [23,24]

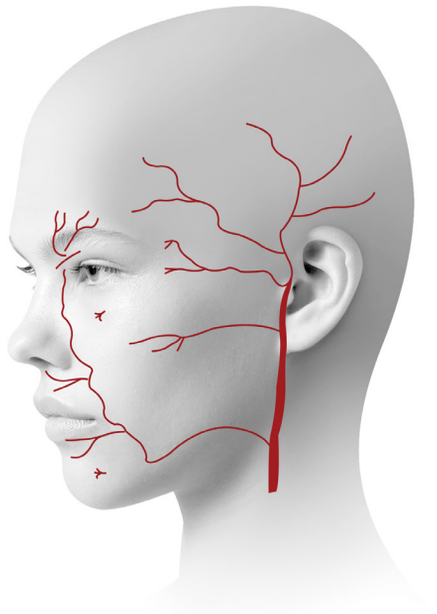


Figure 7: The course of a. facialis on the face

The a. facialis is the main branch of the a. carotica interna supplying the face and branches off from the external carotid artery at the mandibular corner, winds around behind the submandibular gland and reaches the face by turning the mandible in front of the masseter muscle. The facial artery is accompanied by the facial vein. After turning the mandible about 1 cm in front of the masseter muscle, the facial artery follows a very sinuous course and reaches the inner canthus of the eye. It descends deep into the perioral muscles about 1.5 cm from the lateral edge of the lip and travels about 15 mm deep. It also passes subcutaneously about 0.5 cm from the edge of the nose. During its course, the first branch it gives at the edge of the mouth is a. labialis inferior. It then gives the superior labial artery and lateral nasal artery in the oral commissure. The superior and inferior labial arteries join their opposite counterparts in the midline, anastomose and give off numerous small branches into the orbicularis oris muscle. The superior labial artery runs between the mucosa and the orbicularis oris muscle at the level of the vermillion. It gives cutaneous, mucosal and vermillion branches from this main branch. The inferior labial artery runs deep to the alveolar border, between the orbicularis oris muscle and the lip depressors. The lateral nasal artery runs between the nose and cheek and supplies the nose with superior and inferior branches. The lateral nasal artery passes through the nasolabial sulcus and the lateral margin of the nose and reaches the eye as the angular artery in the medial canthus. During its course, numerous anastomoses develop between the facial artery, superficial temporal artery and maxillary artery. The angular artery is located 6-8 mm from the medial canthus, 5 mm from the lacrimal gland. The angular artery anastomoses with the supraorbital, supratrochlear and dorsal nasal arteries.

The facial venous system parallels the arterial distribution. The temporal and lateral forehead drains into the superficial temporal vein. The middle part of the forehead drains into the supraorbital and supratrochlear veins, which in turn join the ophthalmic venous system and the angular vein. The angular vein runs along the lateral margin of the nose and then receives drainage from the superior and inferior labial veins to form the anterior facial vein. The anterior facial vein crosses the mandible behind the facial artery and empties into the internal jugular vein.[23]

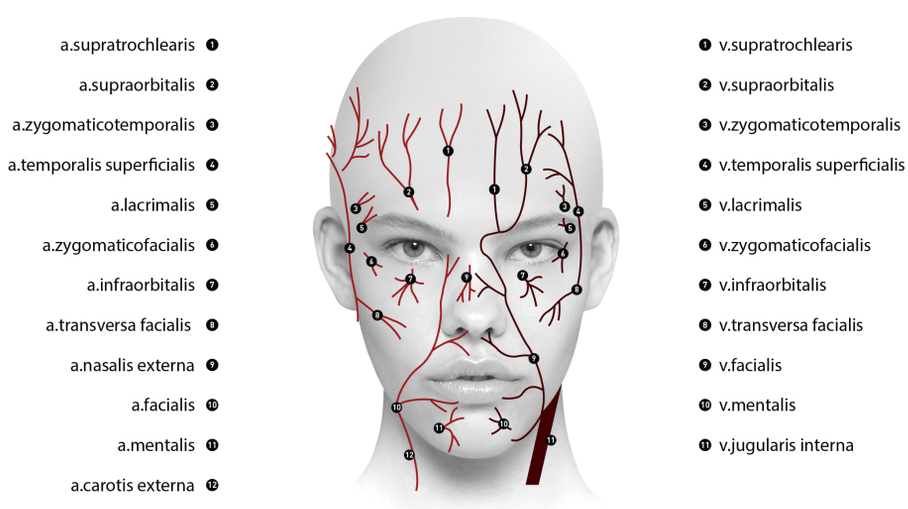


Figure 8: View of facial arteries and veins

The facial skin is innervated by branches of the three main branches of the n. trigeminus, except for the angle of the mandible, which is innervated by the n. auricularis magnus, and a small area over the parotid gland. Sensory innervation is provided by the n. ophtalmicus of the forehead, the n. maxillaris of the midface and the n. mandibularis of the mandible and preauricular regions. The external ear and the submandibular region are sensed by the branches of the plexus cervicalis.

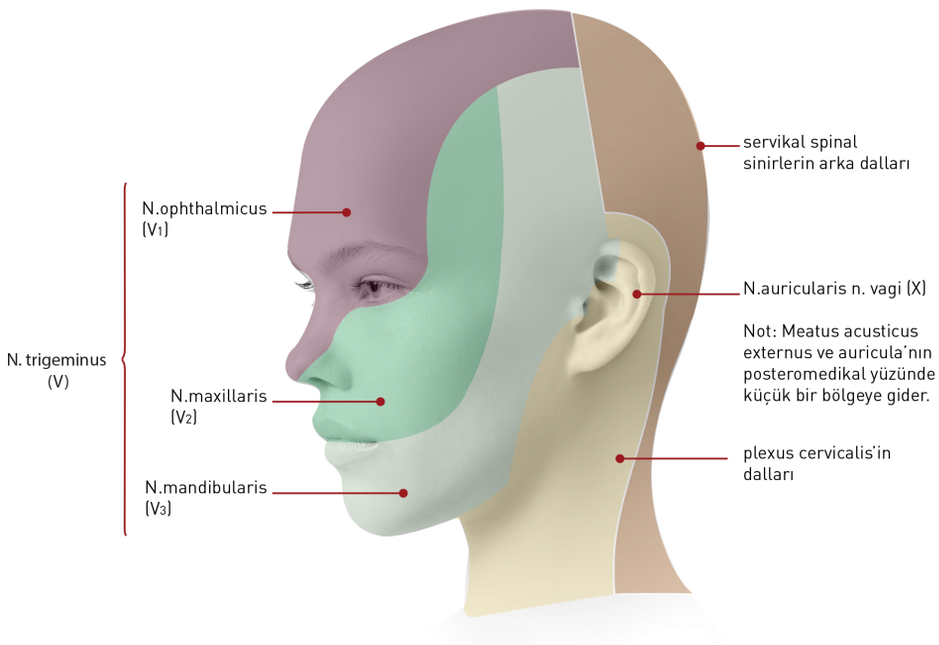


Figure 9: Sensory dermatomes on the face

The facial muscles are embedded in the superficial fascia and most of them start from the skull bones and terminate in the skin. Facial muscles function as sphincters or dilators of the eye, mouth and nasal cavities. The secondary function of facial muscles is to change facial expression. All facial muscles develop from the second pharyngeal arch and are innervated by the n. facialis.27 A notch in the m. zygomaticus major, one of the mimic muscles, causes dimpling of the face. Wrinkles on the face occur with depressions due to the tension in the skin caused by the contraction of the muscles. These wrinkles decrease when the muscles relax.

While a young face is characterized by a smooth transition between subcutaneous tissue compartments, contour changes between these regions are seen with aging. This may be due to volume loss as described by Lambros or to changes in specific compartments due to various factors. Changes in the ligaments over time are insufficient to explain this condition and the fat compartments should also be carefully evaluated. While the M. zygomaticus lubricates an important fixation of the major three compartments, the buccal fat layer plays an important role between the lateral and medial cheek compartments. In studies, it has been observed that adipose tissue is divided into many compartments with advancing age. In cadaveric studies, it was also seen that the nasolabial fold was altered by dissecting the nasolabial fat and shifting it to the medial cheek area. Therefore, the fat layer in the lower jaw plays an important role in facial reconstruction. [26]

2.2-Anatomy of the Neck

The neck is the region between the lower edge of the corpus mandibula, the upper edge of the clavicula and the incisura jugularis. It contains many important anatomical structures because it provides the connection between the head and the trunk. Structures such as trachea, esophagus, thyroid and parathyroid glands, a. carotica communis, a. subclavia, v. jugularis interna and externa, medulla spinalis, n. vagus, n. accesorius, plexus cervicalis, cervical sympathetic chain are located in this region. Since it contains many vital structures, there are serious complication risks in cases requiring surgical intervention.

The natural course of the cleavage lines of the neck skin (sulci cutis) is constant and almost horizontal around the neck. The clinical significance of this is that an incision along the sulcus cutis line will heal as a narrow scar, whereas an incision crossing the sulci cutis lines will heal as a wide or folded scar.[12] There are two fasciae under the skin of the neck, deep and superficial. The superficial fascia surrounds the platysma, cutaneous nerves, v. jugularis anterior, v. jugularis externa and superficial lymph nodes. For this reason, it has a more important place especially in aesthetic surgical interventions to be performed in the neck region. The deep fascia is divided into 3 regions and surrounds muscle groups. The deep fascia is less important in aesthetic surgical interventions.

The platysma is a thin layer of muscle embedded in the superficial fascia of the neck. It is innervated by the cervical branch of the n. facialis. It pulls down the mandible, lower lip and corner of the mouth. The relaxation of this muscle with the effect of aging also has an effect on sagging in the neck. The operation known as neck lift surgery is performed by removing excess fat tissue in the area and increasing the tension of the platysma muscle.

2.3-Hand Anatomy

After the face, the hands are the most visible body part in contact with the outside world and are one of the indicators of physical aging in individuals. Hands are of great importance both aesthetically and sociologically. A long, slender hand is considered beautiful and elegant. Nails are an element that complements the beauty of the hands. With healthy nails, the elegance of the hands stands out very much. Skin aging is a complex biological process caused by internal or external factors or a combination of them. Genetic predisposition, exposure to ultraviolet (UV) rays, environmental factors are important in hand aging. Hand beauty is as valuable as facial beauty and necessary precautions should be taken to protect it.28 Conditions such as decreased muscle mass, decreased active use of hands, malnutrition play an important role in aging of hands .[29]

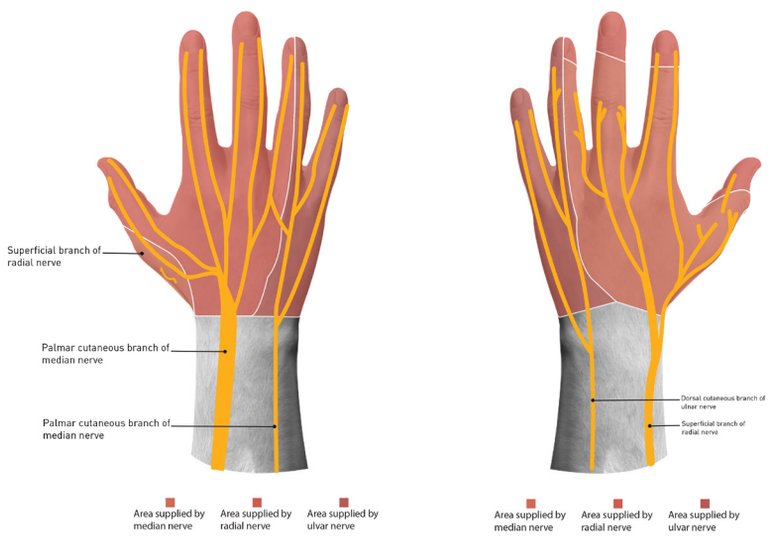


Figure 10: Nerve innervations of the palmar and dorsal surfaces of the hand

The hand is the most active and important structure of the upper extremity and its anatomy and functional biomechanics are very complex. The hand undergoes many physiologic and anatomic changes with aging. When we examine the hand anatomically, the forearm bones ulna and radius articulate to the wrist bones. The bones in the wrist are 8, 4 proximally and 4 distally. The distal bones articulate with the metacarpal bones. A large number of ligaments and tendons that provide the hand with high mobility are attached to this area. There are also carpal and ulnar canals between these bone structures. Important nerve and vascular structures also pass through these canals. The arterial supply of the hand is provided by the a. ulnaris and a. radialis, while the sensory innervation is provided by the n. radialis, n. ulnaris and n. medianus. The venous return of the hand is via the deep and superficial veins forming the v. basilica and v. cephalica. Veins show anatomical variations from person to person and even between the right and left hand. For this reason, hand veins can also be used for biometric identification in forensic medicine. [30]

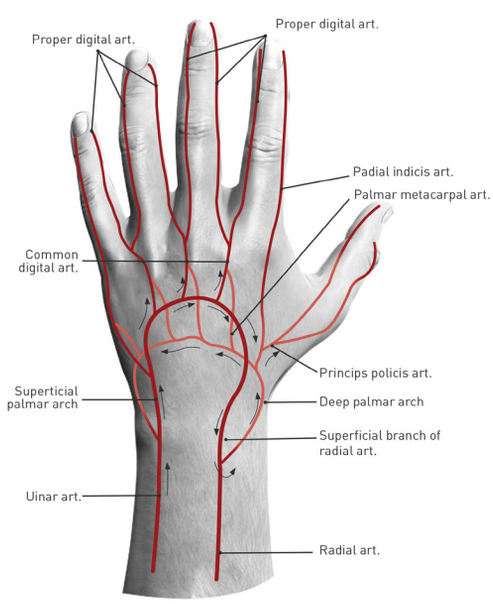


Figure 11: Arterial blood supply to the hand

The skin of the palm of the hand (Palma manus) is thick and hairless and is connected to the deep fascia beneath it by numerous fibrous bands. There are flexion lines where the skin is mobile, not exactly where the joints are. The wrist also has numerous sweat glands. The deep fascia of the wrist and palm is thickened to form the retinaculum musculorum flexorum and the aponeurosis palmaris. The skin of the dorsum of the hand (dorsum manus) is thin and hairy and can move easily over tendons and bones. The sensory nerve of the skin comes from the ramus dorsalis of the n. radialis.[27]

Hands sustain more minor injuries such as abrasions, cuts and burns throughout life than other organs. The healing of wounds on the hands also slows down with age due to decreased mitotic activity and keratinocyte regeneration. The decrease in capillary loops also plays a role in this situation. The dorsum of the hand, which has better skin than the palm of the hand, becomes thinner with age, resulting in drier, more fragile and delayed healing of the skin of the hand. The most obvious appearance of hand aging is wrinkles and decreased elasticity. The main cosmetic problem in the hands is sagging skin, prominent veins and pigmentation changes that occur with aging. The main reason for this is that the dermis and epidermis, which rest on a thin layer of hypodermis, lose their thickness and elasticity.[29]

2.4-Principles for Creating the Golden Percentage

In ancient Greece, the meaning of beauty was questioned and it was thought that the perfect harmony between the structures that make up the world was due to this ratio. For centuries, this ratio has been referred to as the Golden Ratio. From the Egyptian pyramids to da Vinci's Vitrivian Man, this ratio was used in many important works. In nature, this ratio appears many times from cones to snowflakes, snail shells to sunflowers. This ratio is also encountered structurally in the human body. From the bronchial tree of the lung to the fingers of the hand, from the renal tubules to the hepatic Glisson's triangle, this ratio is seen in many places. On the human face, this ratio has inspired and been used in many works. Although the Greek mathematician Euclid was the first to define this ratio, the ratio 1/1.61803399 was discovered by Filius Bonacci and the term "phi" and the symbol ϕ were defined by Mark Berr in the 20th century. [31,32]

Although there are many scientific studies comparing the golden ratio on the face with the perception of beauty, results have been reached about the clear connection between these two concepts. While some studies have shown that the perception of beauty increases as the golden ratio is approached, some studies have concluded that the perception of beauty is independent of the golden ratio. This point should not be ignored that there are many factors such as differences in the methods used and the fact that they were selected from different sociocultural societies. However, when we look at the common result in the studies, it is seen that beauty and being healthy are indisputably linked. When unattractive facial features are evaluated, it has been shown that emotional and psychological states also have a great influence. Especially people at an early age have greater problems with unattractive facial features associated with medical problems. [12]

While calculating the golden ratio on the face, many different proportions such as the ratio of the length of the face to the width of the face, the ratio of the distance of the midpoints of the eyes to the width of the mouth, the ratio of the distance between the eyes to the width of the face, the ratio of the forehead area to the length of the face have been studied. Since different ratios are taken as the basis in all studies, there are many different methods that the practitioner can use when making an assessment.[33]

As there is no universal consensus on the golden ratios, it also creates a wide range for the procedures since there are many studies that can be consulted before the application is made. For this reason, it will be useful to exchange ideas about the procedure to be applied to the patient and to apply the procedure after reaching a consensus with the patient about its possible results.

2.5-Current Treatment Procedures

2 published studies have stated that CaHA shows effect by applying more volume compared to other dermal fillers. For example, in a study where CaHA was applied to one half of the face and collagen to the other half, when the materials used to see the optimal correction were compared, 2 times the volume of collagen was needed to see the effect of CaHA. In another study, it was argued that 30% less volume of application was required in CaHA fillers compared to HA fillers.[34]

Current hand rejuvenation procedures include topical agents, laser resurfacing and peeling procedures, sclerotherapy, fillers and fat injections to reverse volume loss due to fat atrophy. Fat grafting is the best autogenous way to restore youth in the hands; however, it is an invasive, donor site- and anesthesia-dependent, time-consuming and inconsistent procedure with the need for frequent touch-ups after the procedure18. Dermal fillers are a viable option for physicians to restore lost volume in aging hands. Combinations of hand rejuvenation with injectable fillers and mesotherapy have become very popular in the last two decades. Fillers containing CaHA fillers have been used more frequently in the treatment of hand aging since the approval of the United States Food and Drug Administration (FDA) for calcium hydroxylapatite treatment in this anatomical region.[17]

2.6-Preparation of NOVUMA ®

The NOVUMA® injectable implant is supplied sterile and apyrogenic in a syringe packaged in foil pouches placed in a box for easy storage. Each unit consists of a pre-filled syringe containing the NOVUMA injectable implant. Do not use if the packaging and/or syringe is damaged or if the syringe end cap or syringe plunger is not intact.

Remove the foil pouch from the carton. Scrape or crimp the needle pack to expose the body. Remove the Luer syringe cap from the distal end of the syringe before inserting the needle. The NOVUMA® injectable implant

syringe can be attached by twisting the needle into the Luer lock connection. The needle must be securely attached to the syringe and filled with NOVUMA® injectable implant. If excess implant is visible on the surface of the luer lock connections, it must be wiped clean with a sterile gauze swab. Gently push the syringe plunger until the implant material comes out of the needle tip. If the luer connection is leaking, remove the needle and clean the surfaces of the luer connection. In some cases, the syringe and needle may need to be replaced.

In cases where NOVUMA® ready-to-use implant needs to be diluted with saline, the dilution card in the user manual should be carefully examined and the instructions on the card should be followed during the application. Since the NOVUMA® syringe has a volume of 1.5 cc, it is not suitable for dilution. If NOVUMA® is to be diluted, the contents should be drawn into a 5 cc sterile syringe with Luer Lock using the sterile connector in the box. In order to perform the dilution process, a syringe with an equal volume of saline withdrawn in a volume suitable for the desired dilution rate should be attached to the other end of the connector, followed by the transfer of the entire content between the syringes connected to the connector at least 30 times. It is important to ensure that the syringe contents are completely homogenized during dilution.

If the product is to be used as diluted, the recommended dilution rates and the thickness of the skin to be applied should be taken into consideration. In the same application area, thin skins may require more dilution than thick skins. For example, 1:2 to 1:4 dilution is recommended in the neck area. While 1:2 dilution ratio may be sufficient for thick skin, 1:4 dilution ratio will provide better cosmetic results in thin skinned patients.

Do not mix NOVUMA®, with other dermal fillers or neurotoxin products. There are no reported adverse effects related to the concomitant use of NOVUMA®and Youth Series® products.

2.7-Patient Preparation

Pre-procedure applications should be explained to the patient in detail. The products to be used, the method of application, possible results, possible undesirable effects, post-procedure care and follow-up processes should be thoroughly explained to the patient. No application should be performed without the written consent of the patient. Since the result of the application depends on multifactorial factors, the patient should be informed in a way that avoids guaranteeing a definitive result.

A complete anamnesis should be taken. Systemic diseases, regular medications, history of keloid and allergy, history of previous surgical operations and dermal fillers, family history should be questioned.

If the patient has no contraindications and with the appropriate opinion of the treating physician, it is recommended to discontinue drugs that reduce blood viscosity such as NSAIDs and aspirin one week before the application.

The patient does not need to be hungry for the procedure. The patient may have taken oral food until 2-4 hours before the procedure. The patient should not discontinue medication for systemic diseases and should receive treatment during routine hours. There is no restriction on the patient's oral food intake after the procedure.

Before the procedures to be performed on the face, the patient's hair should be collected and the face should not be covered with hair so that the forehead area and ears are completely valued with a hair band.

2.8-Preparation of the Application Area

The area to be treated must be hygienic as it is an environment where medical intervention will be performed. The likelihood of infective organism transport from surfaces such as floors, walls, furniture or medical equipment is low. However, clinical evidence has shown that poor environmental hygiene and the transport of microorganisms can spread many nosocomial infections.[35]

It is recommended to choose a well-lit place for the application area. It is recommended that the room be ventilated for at least 10 minutes before the procedure. It is important to ventilate the room for at least 10 minutes after the procedure to prevent cross-contamination between patients.

The treatment tray should contain all medical equipment that may be needed during the procedure. Personal protective equipment, Luer Lock syringes, needles or cannulas, sterile gauze, aseptic solutions, erasable marking pen, saline, etc. should be available in the area close to the physician or nurse.

All products to be injected under the skin in the patient must be sterile. Actions that will disrupt the sterilization of the products should be avoided. Needles and cannulas must be replaced after non-sterile contact with needles and cannulas.
The application area should be wiped with solutions containing chlorhexidine with a sterile gauze pad and wait for 20 seconds. At the end of the waiting period, dry with sterile gauze. This process should be repeated if necessary.

2.9-Marking the Application Area

Correct marking of the area to be treated before the procedure will both increase the chance of success of the procedure and reduce the risk of complications. Markings can be made with erasable skin marking pens. Important anatomical structures and the area to be treated can be marked. Especially due to the risks of intravascular injections, drawing the anatomical locations of arterial structures will increase the success of the procedure. This step is also important in terms of informing the patient about the area to be treated. Marking the injection sites and marking the application site is recommended as a guide for the areas to be applied according to the technique to be applied.

When marking the facial area, a line is first drawn from the lateral eye to the mandibular corner to separate the mobile and stable areas of the face. The parts medial to the line are mobile due to mimic muscles and the parts lateral to the line are immobile areas. Afterwards, the injection entry points for the application areas and the areas where the application is planned to be performed are marked. The lateral part of the zygomatic arch and the corner of the mandible can be selected for application. If the application is to be performed in the nasolabial sulcus and Marionette lines, the patient is asked to smile and make a "u" sound, and the necessary entry points for the application are determined by marking the lateral part of the mobile area.

Before marking on the neck, the patient is asked to extend the head. A line is drawn from the center of the mental region to the incisura jugularis. Then a vertical line is drawn from both mandibular corners to the midclavicular line. Two more vertical lines are then drawn through the center of the lines. Two horizontal lines are drawn one centimeter above and below the cartilago tiriodea. The points where these lines cross the vertical lines can be used as injection entry points.
Before marking in the hand, the distal metacarpal bones are palpated. This border is accepted as the distal border and lines are drawn between the metacarpal bones to form a cone to meet at the level of the carpal bones.

When marking the arm area, the midline of the humerus is found, and the injection point is determined at the point where the medial side crosses the anterior axillary line.

When marking the knee, a horizontal line is drawn 2 centimeters above the proximal end of the patella. The injection site is determined so that the midpoint of this line is cut perpendicularly with an imaginary line starting from the protuberentia tibialis and passing upwards. The areas to be injected proximally from this point are marked.

If the application is to be performed around the umbilicus, a straight line is drawn above and below the umbilicus, similar to the Abdominal Median and Sub-umbilical Median (GÜGAM) incision line, and the line is given an oval shape around the umbilicus. Horizontal lines are drawn leaving a distance of 1 centimeter from the upper and lower border of the umbilicus. The intersections of these lines can be used as injection sites.
If the application is to be performed in the gluteal region, the gluteal region is divided into four quadrants with two lines that cut each other perpendicularly. Then, lines are drawn 2 centimeters parallel to these lines and the intersections can be used as injection sites.

2.10-Application Techniques
NOVUMA® should be administered in small amounts with low force. Supraperiosteal application should be preferred for deep injections. Application of more than 0.2 cc volume to a single point should be avoided. Although the risk of side effects decreases as the needle or cannula size decreases, the risk of clogging of the injector increases. As the needle or cannula size increases, the risk of ecchymosis increases, but the risk of injection into the intravascular space decreases. If unexpected resistance is encountered during the application or if the patient describes unexpected and increased pain, the application should be stopped.
In subdermal or supraperiosteal planes, the administration volume should be less than 0.2 cc and should always be administered retrogradely to avoid damaging vascular structures. If the patient reports increased or radiating pain, the needle position should be changed. Intraoral applications are not recommended due to the inability to ensure complete sterility at the injection points on the mucosa and the risk of biofilm formation. If intraoral application is absolutely necessary, hydrogen peroxide can be applied to the area before application. [36]
There are no adequate scientific studies on the co-administration of lidocaine and epinephrine with other implants containing CaHA. There are no scientific studies on the co-administration of lidocaine and epinephrine with the NOVUMA® injectable implant.
NOVUMA® injectable implant can be administered using a needle or a blunt-tipped cannula.
If CaHA is to be applied for filling wrinkles and deep lines, it is recommended to be applied in the subdermal plane. The injection depth can also be made in the subcutaneous area above the periosteum. If it is desired to add volume to the face, it can also be done just above the periosteum. Application in the periosteum does not stimulate bone formation in this area.
Depending on the applied area, CaHA can be applied retrogradely in the form of linear, fan or cross-hatching. In supraperiosteal applications, the desired effect is usually achieved by bolus application and then massaged and distributed. Injection volume may vary according to the anatomical plan, size and characteristics of the patient. It is necessary to check that there are no palpable lumps by massaging. While some physicians routinely massage the application area, some physicians avoid it because of the risk of unwanted shapes, edema and erythema. When the scientific literature is examined, there is no consensus on this issue.
Although aspiration is thought to be a good method to avoid intravascular injection, 10-second aspirations with 0.5 ml negative pressure with undiluted CaHA injectors cannot prove that there is no intravascular space. In aspiration tests with diluted CaHA injectors, positive results were obtained in 1 second with needles smaller than 27G, 3 seconds with 27G needles and 7 seconds with 23G needles. Some studies show that a waiting time of 5 seconds in slow retractions increases the accuracy of aspiration tests.[37]

2.10-1. Face
After marking as described in Section 2.9, an injection entry hole is created with an 18G injector needle for the entry of the 25G cannula from the points determined as injection points. Then, NOVUMA application is performed with the 25G cannula. During the application, retrograde application with fan technique is recommended from the marked injection points.

In the application to be performed on the face, the application volume will vary according to the needs of the patient in the zygomatic region, mandibular region and nasolabial grooves. It is recommended to use 1.5cc NOVUMA® product for each side of the face. 1.5 cc NOVUMA® can also be used on the entire face by making a 1:1 dilution with saline.

During application, it is important not to inject into arterial structures and fat pads in the malar-nazolabial region. Injections into arterial structures may cause coagulation necrosis due to arterial occlusion. When injected into the malar fat pads, the risk of edema development in the patient is very high. NOVUMA is not recommended for the eye area including eyelids, glabellar region, oral mucosa and lips due to the high risk of side effects.

The face is checked for sensory and motor nerve loss. The procedure is completed after possible complications are evaluated. After the procedure, it is sufficient to press the needle entry site with cotton until hemostasis is achieved. Afterwards, a round injection tape can be applied to the injection site with the recommendation that the patient should remove it after 12 hours.

2.10-2. Periorbital Region
NOVUMA® injectable implant application in the periorbital region is not recommended due to the lack of sufficient scientific studies and the risk of adverse effects. In cases where application in the periorbital region is required, CORINTHA® from Youth Series products can be applied.

2.10-3. Lips
NOVUMA® injectable implant application in the lips is not recommended due to the lack of sufficient scientific studies and the risk of adverse effects. In cases where application is required in the periorbital region, TUSCAN® or IONA® from Youth Series products can be applied.

2.10-4. Hand
The licensing process for the use of NOVUMA for applications in hand has not yet been completed, but other implants containing CaHA are safely used, and there have been no major adverse effects reported related to the off-label usage of NOVUMA. In this region, the patient should be informed about this usage situation, and Informed Consent must be obtained.

The patient is placed in a sitting position with hands placed on the treatment table. The hands are raised to the level of the heart. Treatment areas are determined on the dorsum of the hand. The border of the injected cavity is the fifth metacarpal bone laterally, the second metacarpal bone medially, the dorsal wrist crease proximally and the metacarpophalangeal joints distally.

The outline of the injection site is marked with a skin pencil, and the injection site is wiped twice with gauze with chlorhexidine solution. An 18 G needle is inserted in the center of the dorsal wrist crease to create the cannula port.

The skin on the dorsum of the hand is squeezed and elevated with the non-injecting hand to facilitate separation of the skin from the vascular and tendinous structures at the puncture site. The CaHA-lidocaine mixture is injected linearly into the areolar plane between the subcutaneous layer and the superficial facia of the hand using the prepared NOVUMA® injector (described in detail in Section 2-6) 25G 1.5-inch Cannula.

The injection is made by injecting content in an inverted triangle shape by retracting the cannula from distal to proximal. The injection site is massaged manually until the filler spreads evenly. Bleeding control is performed after the application. Arterial filling time control is performed. Hands are lowered below the heart level; venous return is checked. Sensory and motor nerve loss in the hand is checked. The application is completed after possible complications are evaluated. After the procedure, it is sufficient to press with cotton until hemostasis is achieved at the needle entry site. Afterwards, round injection tape can be applied to the injection site with the recommendation that the patient should remove it after 12 hours. Patients are advised to wear non-tight cloth gloves for the following 3 days and to keep their hands elevated if possible.

2.10-5. Neck
The licensing process for NOVUMA for application in the neck area has not yet been completed and there are no major adverse effects reported due to the safe use of other implants containing CaHA and "off-label use" of NOVUMA. In this region, the patient should be informed about this use case and informed consent must be obtained.

As explained in detail in Section 2.9, injection entry points are created with an 18G needle from the injection points after marking. A 25G cannula can be attached to the NOVUMA syringe and retrograde application can be performed with the fan technique. Short linear applications with a needle can also be an alternative method. The dilution ratio can be decided according to the patient's skin thickness. Dilution can be made up to 1:4 in thin skin. For thick skin, a dilution ratio of 1:2 will be sufficient. It is recommended to use 1.5 cc NOVUMA in total for the application. Changes in application volumes may be necessary according to the needs of the patient.

Injections to be made in the neck area should be done with attention to important anatomical structures, and very deep and very superficial applications should be avoided. The product should be applied to the entire application area, and papules should not be created with punctate bolus applications.

It is checked whether there is sensory and motor nerve loss in the application area. The application is completed after the possible complication is evaluated. After the procedure, it is sufficient to press the needle entry site with cotton until hemostasis is achieved. Afterwards, a round injection tape can be applied to the injection site by advising the patient to remove it after 12 hours.

2.10-6. Decolletage Area
The licensing process for NOVUMA for application in the décolleté area has not yet been completed and there are no major adverse effects reported due to the safe use of other implants containing CaHA and "off-label use" of NOVUMA. In this area, the patient should be informed about this use case and informed consent must be obtained.

In scientific studies, there are established guidelines for CaHA application in the décolleté area. If NOVUMA is to be applied in the décolleté area, it should be applied in the subdermal plan. Short linear injections with a needle or retrograde injections with a cannula can be performed. Depending on the patient's skin thickness, 1:2 to 1:4 dilution ratios can be applied. Dilution up to 1:4 can be made in thin skin. For thick skin, a dilution ratio of 1:2 will be sufficient. 0.75 cc or 1.5 cc NOVUMA can be applied. [18]

It is checked whether there is sensory and motor nerve loss in the application area. The application is completed after the possible complication is evaluated. After the procedure, it is sufficient to press the needle entry site with cotton until hemostasis is achieved. Afterwards, a round injection tape can be applied to the injection site by advising the patient to remove it after 12 hours.

2.10-7. Arm
The licensing process for NOVUMA for application in the arm area has not yet been completed and there are no major adverse effects reported due to the safe use of other implants containing CaHA and "off-label use" of NOVUMA. In this area, the patient should be informed about this use case and informed consent must be obtained.

If NOVUMA is to be applied in the arm, it should be applied in the subdermal plan. NOVUMA can be administered in this area with a dilution ratio of 1:1 or 1:2 using the short linear line technique. When selecting the injection entry point, while the arm is in the anatomical position, an injection entry area can be created with an 18G needle at the intersection point of a linear line drawn from the anterior-axillary line and a horizontal line passing through the midline of the humerus and application can be made with a 25G cannula.

It is checked whether there is sensory and motor nerve loss in the application area. The application is completed after the possible complication is evaluated. After the procedure, it is sufficient to press the needle entry site with cotton until hemostasis is achieved. Afterwards, a round injection tape can be applied to the injection site by advising the patient to remove it after 12 hours.

2.10-8. Knee
The licensing process for NOVUMA for application in the knee region has not yet been completed and there are no major adverse effects reported due to the safe use of other implants containing CaHA and "off-label use" of NOVUMA. In this area, the patient should be informed about this use case and informed consent must be obtained.

If NOVUMA is to be applied in the knee area, it should be applied in the subdermal plan. The product can be applied with a cannula using the retrograde fan technique or with a needle using short linear routes. The treatment recommendation is to apply from the area proximal to the patella. When determining the injection entry point, go 2 centimeters proximal to the proximal edge of the patella, create an injection entry area with an 18G needle at the level of the protuberintia tibialis and apply with a 25G cannula.
It is recommended to use 1.5 cc NOVUMA in total for both knees. There is no consensus on the dilution ratio, and there are applications that have used a ratio of 1:1 to 1:4. 18

It is checked whether there is sensory and motor nerve loss in the application area. The application is completed after the possible complication is evaluated. After the procedure, it is sufficient to press the needle entry site with cotton until hemostasis is achieved. Afterwards, a round injection tape can be applied to the injection site by advising the patient to remove it after 12 hours.

2.11-Use of Needle or Cannula in Practice
NOVUMA® injectable implant can be applied using a needle or a blunt-tipped cannula. There are no scientific studies on the differences between needles and cannulas. Although cannulas cause less tissue trauma, the risk of occlusion is higher with a higher volume when entering the vascular plan. Needles are a more popular choice because they provide a single puncture. [37]

The use of 22-25G blunt-tipped cannulas reduces the risk of intravascular injection in high-risk areas but is not 100% safe. Cannulas larger than 25G require greater force to enter the intravascular space than needles, whereas 27G and 30G cannulas are closer to needles. In order to reduce the risk of intravascular injection, another option is to apply the needle or cannula retrogradely by continuously moving the needle or cannula to avoid applying a large high volume to a point. The use of local anesthetics containing epinephrine will prevent filling entry because it will cause contraction in the vessels and reduce the vessel diameter. It may also conceal occlusion findings. Hydrodissecting the tissues with saline gives favorable results in many areas. It provides space for saline NOVUMA® and provides the physician with ease of application and reduced risk of complications.[38]

There are publications recommending the use of CaHA with 25G and 27G needles due to its relatively high viscosity. [37]

Since both application techniques have advantages over each other, and no one method is generally accepted in the scientific literature to be superior to the other, applications can be performed with both needle and cannula.

3.AFTER APPLICATION
This section contains information about the process that starts after NOVUMA® injectable implant application.

This section includes recommendations on the issues to be considered by the physician and the patient after the application, information about the treatments that may be required after the application, the control processes of the patient after the application, the disposal of the materials used in accordance with waste management, and the issues to be considered in the process of photographing the procedure by the physician if patient consent is obtained.

3.1-Care of the Application Area
Dressing in the application area after the application is not required under normal conditions.

After the application is completed, it should not come into contact with water for 24 hours to prevent infection from the application entry holes.

Ice can be applied to the application area to reduce hyperemia and edema that may occur within 48 hours following the application. Ice application should not exceed 10 minutes per hour and ice should not come into direct contact with the skin. Ice application can be done with materials such as ice packs and towels that can act as a barrier to prevent the direct contact effect of ice on the skin.

After the application, movements that may affect the distribution of NOVUMA® in the application area in the first 72 hours should be avoided. Patients should be informed about this according to the application area.
It is not recommended to perform other applications (laser, epilation, peeling, etc.) in the application area for 4 weeks.

3.2-Patient Considerations
In order to see the changes in the tissue and the effectiveness of NOVUMA® after the application, it is of great importance not to consume cigarettes and other tobacco products.

Facial massage and procedures involving deep scrubbing should not be performed for at least 2 weeks. Treatments used for systemic diseases (hypertension, diabetes, etc.) should be continued. Especially in diabetic patients, attention should be paid to blood glucose levels as wound healing is affected.

After the procedure, a sunscreen with a factor of at least 50 (+50 SPF) should be used daily. The sunscreen should be reapplied at least 20 minutes before going out in the sun and every 2 hours.

In the 24 hours following the application, direct sunlight and very hot environments should be avoided, alcohol consumption and heavy exercise should be avoided.

Swelling and redness in the application area is normal for the first 48 hours. Edema due to the injection will disappear within the first 1 week. In cases lasting longer than this period, you should consult your doctor.

Some patients may develop a picture of allergic edema around the face, lips and eyes called angioedema within hours following the application. This picture may regress spontaneously within hours and days or may last longer. If this condition develops, you should consult your doctor immediately.

You should consult your doctor in cases such as pain, loss of sensation, palpable mass, numbness after the application.

Depending on the application, bruising may occur in the application area, you should inform your doctor in case of bruising and the size of the bruise should be monitored if your doctor deems appropriate. In case of bruising, sunlight and activities such as heavy exercise that increase blood pressure should be avoided for faster healing.

After application, gently massage the treated area for 5 minutes, 5 times a day for 5 days.

3.3-Post-Application Drug Treatments
After NOVUMA® application, patients do not need to take any medication regularly.

Paracetamol at a dose not exceeding 2g/day may be prescribed if deemed appropriate by the doctor due to the patient's potential pain related to the application.
For superficial ecchymoses that may develop due to the procedure, pomades containing active ingredients such as mucopolysaccharide polysulfate and heparinoids may be prescribed.

There are scientific studies showing that foods containing hydrolyzed collagen increase collagen thickness and patients may be advised to use them regularly.
Vitamin C and vitamin E play a role in both wound healing and collagen synthesis and can be prescribed as needed.

3.4-Complications and Management
There have been no systemic side effects reported to date after NOVUMA® application. The reported complications have been attributed to errors in application techniques, off-label uses, and patient-related factors. In order to minimize the development of complications, it is important to have a thorough understanding of the anatomy of the application area, to prepare the products properly and to use the correct application techniques.
Complications related to injections during the application are generally similar to all intradermal and subdermal injections.

Erythema: Erythema at the procedure site usually resolves within 48 hours and no complications lasting longer than 1 week have been reported to date. In order to reduce the occurrence of erythema, multiple injections should be avoided, excessive attempts at application correction should be avoided and ice can be applied for 10 minutes starting immediately after application, avoiding direct contact with the skin. Ice application can be repeated at one-hour intervals.[38]

Edema: Edema at the procedure site usually resolves within 48 hours and there have been no reports of edema lasting longer than 1 week. To reduce edema formation, the application site should be kept above the level of the heart for 48 hours after application and ice application should be repeated hourly for no more than 10 minutes.

Pain: Pain at the procedure area is considered normal for the first 4 hours depending on the application. To reduce the occurrence of pain, creams containing local anesthetics can be used in the application area before the application. Long-term pain is not expected after the procedure and paracetamol may be prescribed for patient comfort. In case of pain exceeding 4 hours, vascular occlusion should be evaluated by considering other accompanying findings.

Ecchymosis: It may occur depending on the application. For ecchymosis that will completely resolve within a week, anti-ecchymosis treatments may be prescribed as a result of patient comfort and aesthetic evaluation. Patient-related factors also play an important role in the development of ecchymosis, and these conditions should be evaluated correctly before the application decision is made in patients with coagulation disorders or thrombocytopenic patients.

Hemorrhage: Arterial and venous structures should never be injected. Capillary structures may be damaged due to injection and bleeding in the form of leakage may occur. In these cases, it should be distinguished whether the bleeding is leakage or arterial hemorrhage. In case of a capillary hemorrhage, a few minutes of tampon application will be sufficient. If arterial structures are damaged, further evaluation may be necessary.

Hematoma: Although the development of hematoma after application has not been reported so far, there is a risk of development as a result of damage to vascular structures due to application. The treatments to be applied vary according to the hematoma area and size. If the hematoma can be dispersed with mechanical pressure and hemostasis can be achieved, no major problem is expected except for the development of ecchymosis. However, if large hematoma areas develop as a result of severe trauma to arterial and venous structures and compression signs are observed, surgical evacuation of the hematoma may be required.

Paresthesia: Development of paresthesia after administration is not expected and has not been reported to date. Since the development of paresthesia may be related to the local anesthetics used during administration, it is expected that the paresthesia will regress after the effect of local anesthesia wears off. In the presence of persistent paresthesia, nerve damage during injection should be considered and neurological evaluation should be performed.

Necrosis: There is a risk of developing coagulation necrosis as a result of vascular occlusion due to intra-arterial administration. Although it has not been reported after use of the NOVUMA® injectable implant, there are published cases with other implants containing CaHA. To prevent the development of necrosis, the anatomy of the vascular structures should be well known and care should be taken during application, especially in areas supplied by single arteries. Pratt's 5-P findings may help in the evaluation of necrosis development. These are pain, pulselessness, paresthesia, pallor, poikilothermy, and paralysis.
Although these findings are not always clear, they may be instructive in terms of clinical suspicion. In cases where there is a risk of arterial occlusion, heat should be applied so as not to burn the skin, if the injector is in the occluded vascular structure, iv hydration with saline should be performed, analgesia should be provided, nasal oxygen should be given to increase tissue oxygenation, extrinsic pressure should be avoided, and the occlusion site should be lowered below the level of the heart to improve perfusion.
The patient should be closely monitored for the development of necrosis as a result of occlusion. A case study was published in which a patient with acute angular artery occlusion and secondary transient retinal artery occlusion within 1 hour after the application of other implants containing CaHA was treated with 325 mg oral acetyl salicylic acid (ASA), 40 mg prednisone i.v, 50 mg sildenafil p.o and 60 mg enoxaparin subcutaneously (1mg/kg) and 0.2% glyceryl trinitrate cream. This patient was discharged with a prescription for ASA, sildenafil and 6 days of methylprednisolone after 4 hours of observation and resolution of symptoms.
Hyperbaric oxygen therapy was also recommended. In the follow-up of the patient, it was observed that there were no long-term adverse effects related to the injection. Patients should be prescribed oral antibiotics effective against Gram (+) bacteria due to the risk of infection in necrotic tissues. [39]

Papule or Nodule Development: It may be seen due to the failure of the product to disperse in the connective tissue as a result of superficial applications. Firm massage at fifteen-minute intervals and mechanical distribution of the product is required.
Large nodules can be dissolved with a mixture of lidocaine and saline, although it is very rare for large nodules to form with experienced hands. Up to 0.3 cc of 5-fluorouracil can be mixed with lidocaine in a 1:1 ratio and injected directly into the nodule, reducing fibroblastic activity and breaking the nodule structure. This procedure mechanically disrupts the nodule and prevents future volume creation as it suppresses the biostimulation effect. Steroid application has been largely abandoned and is not recommended because it permanently thins the skin and causes depigmentation. [37]

Infection: It may develop due to the failure to perform necessary aseptic procedures before the operation, patient predisposition, or poor care. Since they usually develop due to Gram (+) cocci bacteria, they are sensitive to penicillin group antibiotics. Infections caused by biofilm-forming infectious agents require treatment with broader-spectrum antibiotics and should be consulted with an Infectious Diseases Specialist.

3.5-Evaluation and Photography of the Application

In medical aesthetic applications, creating objective evaluation criteria is quite challenging. Therefore, there is no universal consensus on the evaluation scales developed. When it comes to assessing the effectiveness of applications, visual assessment is the most commonly used method. For more objective evaluations, the results from evaluation scales and devices that perform skin analysis are used.

When the studies in the scientific literature are examined, it is seen that evaluations are made on 2 main scales.

The first is the evaluation of the application based on the change in the SWRS score, which is discussed in detail in Section 1.2. With this evaluation method, the efficacy of the application can be evaluated after the application in the nasolabial sulcus.

The second is evaluations with the Global Aesthetic Improvement Assessment Scale (GAIS). In this scale, the appearance before and after the application is compared and the change is scored between 1 and 5 points. It should be accepted that the evaluations on the GAIS scale are highly subjective.

Table 3: GAIS Scale

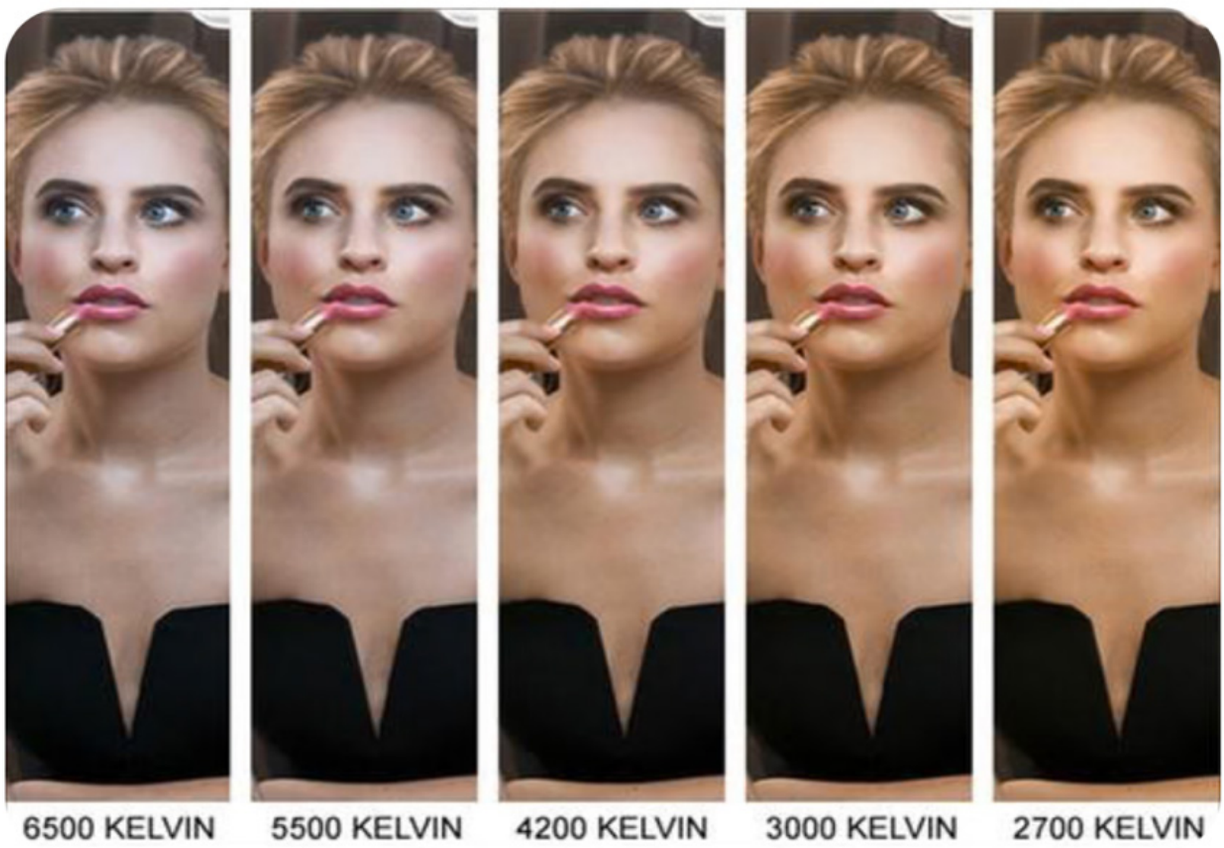
Score	Change	Description.
1	Very Improved	The individual has reached the optimal result.
2	Much Improved	There is significant improvement in appearance but not optimal.
3	Improved	There is improvement compared to before the procedure, but a repeat application is needed.
4	No Change	No difference compared to pre-implementation
5	Worsening	Appearance is worse than before the application.

In the evaluation after NOVUMA® application, it is very difficult to determine objective criteria due to patient, application region and sociocultural differences in the application results. At this point, it is of great importance how much the expectations of the patient and the physician are met. Although the effect starts to be seen immediately after the application, the patient should be reminded that the real effect will start in the 4th-8th weeks and the evaluation should be made at these times. After the application, the optimal evaluation times will be to call the patient for controls on the 7th day, first, third, sixth and twelfth months. The necessity and timing of reapplication at the twelfth month control should be discussed with the patient.

With the written consent of the patient, the procedure may be photographed and video recorded. In the evaluation of the results of the application, photographs are of great importance both for evaluations with other physicians and for guiding the patients who have undergone and will undergo the procedure. At this point, it is important to use the correct photographic techniques.

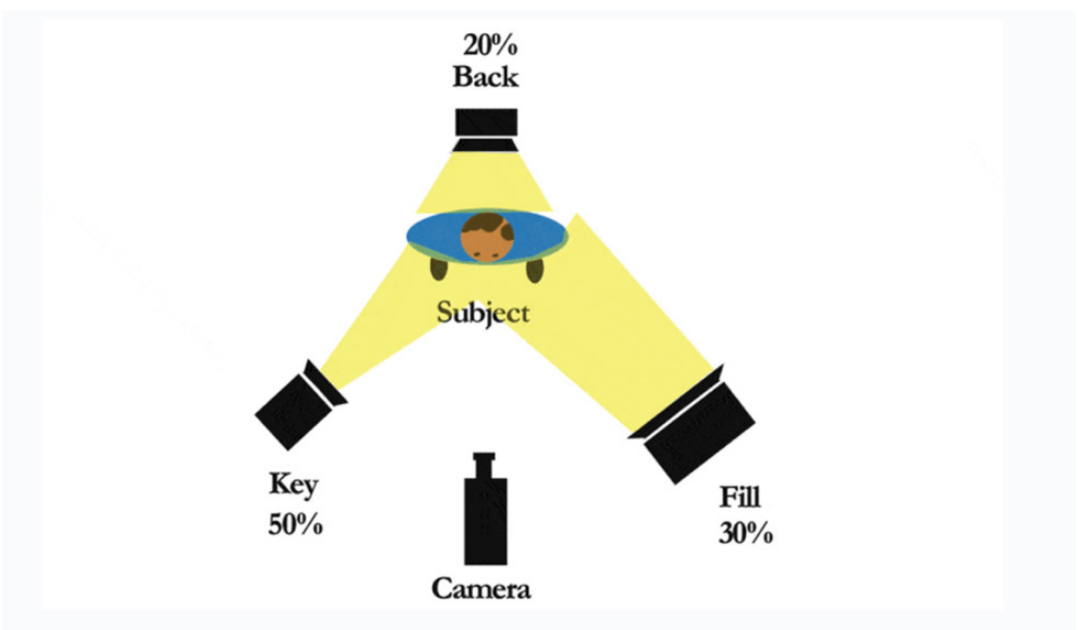
After determining the area to be photographed, a suitable area should be prepared for shooting. One of the most important points is to obtain the correct colors in the photograph by using lights with high CRI (color rendering index) value. As the CRI value approaches 100, the chance of getting the right color will increase.

PICTURE 1: Image of the same object at different CRI values [40]



PICTURE 2: Image of the same photograph at different light temperature values [41]

Daylight has a color temperature between 4000-5000 Kelvin. The lights used should also have these values, which will lead to maximum quality in the photographs to be taken. Using the three-light technique in the placement of the lights will ensure the best results. This method uses two lights positioned behind the camera and one light positioned behind the patient. Assuming that they have equal power, the light powers should be 50% on the back right, 30% on the back left and 20% behind the patient, respectively.



PICTURE 3: Ideal light setting for photography

Written consent of the patient must be obtained for photography.

A white background should be preferred for photography. At this point, white photo backdrops can be used, or it can be done in front of a plain white wall (#ffffff; RGB 255,255,255; RAL 9016). The lights should be positioned at a 45-degree angle to the patient, with one on each side, behind the lens.

Shooting can be done with the right background and sufficient light. The lens (camera, cell phone) should be cleaned in accordance with the manufacturer's instructions before taking the photograph. Photos taken with dirty lenses may be misleading for evaluation.

Photographs can be taken before the application, 15 minutes after the end of the application, on the 7th day, in the first, third, sixth and ninth, twelfth and eighteenth months in the evaluation of the application results. It is important to use the same angle in photographs and the angle of the previous photograph should be carefully examined before taking a new photograph.

The patient's face must be in its anatomical position for facial extractions. Eyes should be open, teeth should be completely closed, lips should be closed, muscles around the mouth and eyes should not be tightened and mimics should not be created. Hair should be gathered with a hair band and should not fall on the face. The center of the imaginary line between the glabella and the tip of the nose should be in the center of the photo frame.

For hand shots, the patient's hand should be positioned on a white background with the dorsal side visible. No accessory (such as watch, ring, bracelet) should be worn on the hand. The photograph should be taken at a distance of 30 centimeters above the hand, forming a 90-degree angle with the surface on which the hand is placed.

3.5-1.Physician Practice Evaluation Form
https://forms.gle/kwhQHrtokhEVu9k69
This form was designed for the physician to share his/her experiences regarding his/her practice. The completion time of the form is approximately two minutes. The content of the form includes general information about the physician, general information about the patient, questions about the application area and method, and questions regarding the physician's satisfaction with the product used.

3.5-2.Patient Practice Evaluation Form
https://forms.gle/p3izAuv8k7NNa3Ww7
This form was created for the patient to share his/her experiences about the application process. The completion time of the form is approximately one minute. The content of the form includes questions about general information about the patient, general information about the physician, the application area and the patient's satisfaction with the application process of the product.

3.6-Waste Management of Used Products
Unused products or waste materials should be disposed of in accordance with the "Regulation on Control of Medical Waste" and "Regulation on Control of Packaging Waste".
Any material that has come into contact with the patient's body fluids should be considered as medical waste.

NOVUMA® syringe and connector must be separated from the cannula or needle as medical waste and disposed of in the red waste bag.

The needle or cannula used in the application should be disposed of in the sharps medical waste box after the application.

The packaging of the NOVUMA® syringe is recyclable and should be disposed of in the recycling bin designated for plastic waste.

After the adhesive part of the patient barcode is attached to the patient's file, the remaining part, which is recyclable, should be disposed of in the recycling bin designated for paper.

The user manual is recyclable and should be disposed of in the recycling bin designated for paper.

The NOVUMA® packaging box is recyclable and should be disposed of in the recycling bin designated for cartons.

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