

RHA® Dynamic Volume for Nasolabial Folds correction

Patient Information Brochure

Please read this document carefully before your treatment, it contains important information about RHA® Dynamic Volume.

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1. GLOSSARY

Note: the terms in the glossary are **bold** throughout the document.

Allergic reaction: allergic reactions occur when a person's immune system (needed to fight infections) overreacts to substances that are harmless for most people. Symptoms could include a rash, sneezing, itching, congestion, or difficulty breathing

Anaphylaxis: a severe **allergic reaction** that needs medical treatment right away

Anesthetic: a medication that reduces pain; it can be added to a cream or a **dermal filler**; sometimes called a numbing medicine

Anticoagulants: medications that thin your blood

Anti-inflammatory: a medicine that reduces pain, heat, redness, and swelling, which are symptoms of inflammation

BDDE: 1,4-butanediol diglycidyl ether, a chemical compound used in very small amount to bind the chains of **HA** together to form a gel

Common Treatment Reaction: reactions that can be expected after injection of a **dermal filler**. It includes bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change in skin color, and itching

Dermal filler: material that is injected under the skin to help smooth and plump wrinkles and folds

Dynamic: able to move, not fixed in place, such as the skin on the face

Granuloma: localized hardening under the skin, like a lump, appearing weeks or months after the injection

Herpes: a virus that causes certain skin conditions, such as cold sores

Hyaluronic Acid (HA): a naturally occurring substance found in the human body which helps maintain skin structure and feel. The HA found in RHA® Dynamic Volume is a different form than the HA found in the human body

Immunosuppressive therapy: medications that reduce the body's normal response to infections, allergens, anything not normally found in the body.

Keloid: a thick tough scar that grows beyond the borders of the original wound.

Lidocaine: a type of **anesthetic** medication that helps reduce pain during injection. The anesthetic medication temporarily (less than 24 hours) anesthetizes the treatment area.

Mepivacaine: a type of **anesthetic** medication that helps reduce pain during injection. The anesthetic medication temporarily (less than 24 hours) anesthetizes the treatment area.

Nasolabial folds (NLFs): the medical term for the wrinkles and fold lines between the nose and the corners of the mouth

Pigmentation disorders: general term to refer to health conditions that affect the color of the skin

Severe common treatment reaction: reaction following an injection with symptoms that caused severe discomfort, compromised the performance of daily activities and for which treatment of the symptoms was needed. The severity is determined by the patient

Streptococcus equi: a bacteria, which does not cause illness in people, used to make the **hyaluronic acid**

Therapy: treatment intended to reduce, heal or cure pain, disease, or physical reaction

Touch-up: an additional injection, performed 2 to 4 weeks after the initial injection. Some patients may require a touch-up treatment to achieve the desired aesthetic results

Treatment Related Adverse Events (TRAEs): any unusual medical occurrence in a subject following the injection which is related to the dermal filler as determined by the doctor. It may be any symptoms, disease or reaction associated with the use of the dermal filler

2. PRODUCT DESCRIPTION

What is RHA® Dynamic Volume?

RHA® Dynamic Volume is an injectable gel (also called a **dermal filler**) used to treat facial wrinkles and folds. It is injected in the moving (**dynamic**) area of the face especially between the nose and corners of the mouth (**nasolabial folds**) (see Figure 1). It is approved for use in adults over 22 years of age.

RHA® Dynamic Volume is produced with **hyaluronic acid (HA)** and using an advanced technology to obtain a soft and long-lasting injectable gel to smooth facial wrinkles and folds. Chains of **HA** are linked together through a chemical reaction triggered by a small quantity of **BDDE** to create the gel texture of RHA® Dynamic Volume. The **HA** of the gel is made from a non-animal source.

RHA®Dynamic Volume contains a small amount of an **anesthetic** medicine (**mepivacaine**), to help reduce discomfort during injection. The effect of the anesthetic is temporary, some discomfort may be experienced due to the injection of the filler during and after the procedure.

Hyaluronic acid (HA) is a naturally occurring substance found in the human body. Your body's own **HA** helps maintain the skin's structure and its natural feel.

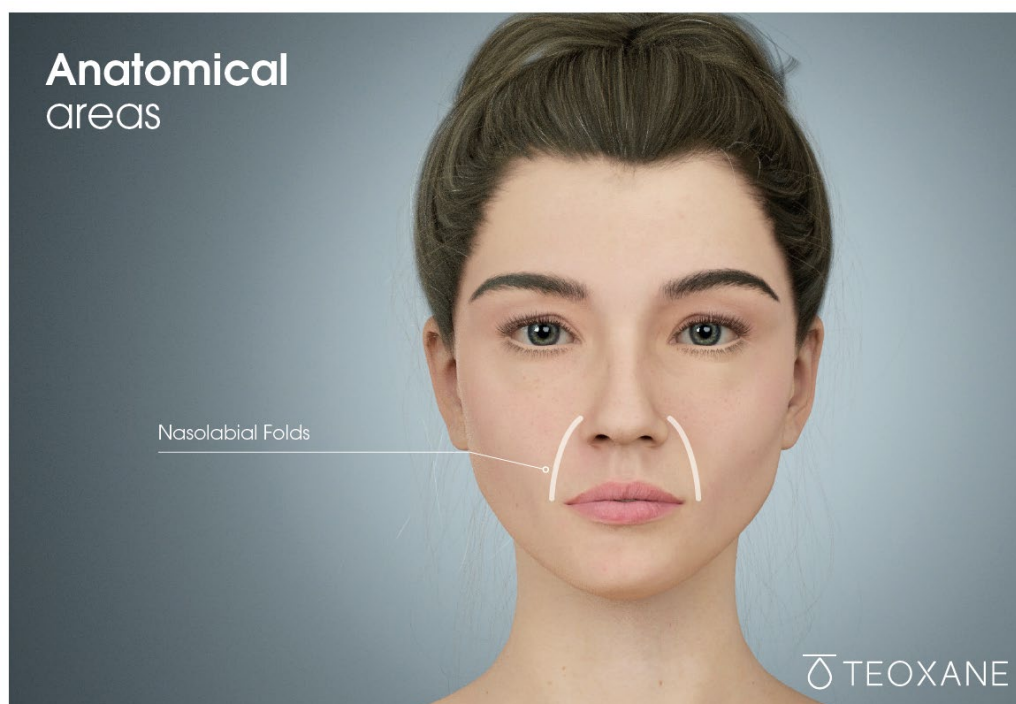


Figure 1: Location of **nasolabial folds**

How does it work?

RHA®Dynamic Volume is injected into the skin with an ultrafine needle to plump the skin to fill in and smooth away wrinkles and folds such as the lines from your nose to the corners of your mouth (**nasolabial folds**).

RHA® Dynamic Volume is not a permanent gel. It slowly goes away as the body absorbs the gel. The smoothing and plumping effect will gradually disappear.

3. CONTRAINDICATIONS

Are there any reasons why I should not receive RHA®Dynamic Volume?

Your doctor will ask about your medical history to see if RHA®Dynamic Volume is right for you. You should not use RHA®Dynamic Volume if you have a history of:

- severe **allergic reactions (anaphylaxis)** or history or presence of multiple severe allergies: an injection of RHA®Dynamic Volume may result in an **allergic reaction**.
- **allergic reactions** to the material (from ***Streptococcus equi***) used to make the **HA** in RHA®Dynamic Volume: an injection of RHA®Dynamic Volume may result in an **allergic reaction**.

- **allergic reactions** to **mepivacaine** or other similar substances such as lidocaine used to reduce pain: an injection of RHA® Dynamic Volume may result in an **allergic reaction**.
- bleeding disorders: any injection, including RHA® Dynamic Volume and other **dermal fillers**, may result in a higher risk of bruising or bleeding in the treated area.

4. PRECAUTIONS

Are there precautions that I should discuss with my doctor?

The following are important treatment considerations that you should discuss with your doctor. These hazards, if not avoided, could result in unsatisfactory results or complications.

- Tell your doctor if you are under 22 years of age. RHA® Dynamic Volume has not been studied in people younger than 22 and the effects are not known.
- Tell your doctor if you are pregnant (or plan to be) or breastfeeding. RHA® Dynamic Volume has not been studied in women who were pregnant or breastfeeding and the effects are not known.
- Tell your doctor if you are taking medicine that reduces your body's ability to fight infection (**immunosuppressive therapy**). Taking this type of medicine may increase the risk of infection following the injection of RHA® Dynamic Volume or other **dermal fillers**.
- Be sure to tell your injecting doctor if you are using "blood thinners" (**anticoagulants**) or any other medications that affect bleeding. Do not stop taking them until you speak with the doctor who prescribed them for you. Tell your prescribing doctor that you are considering having your wrinkles treated with RHA® Dynamic Volume. These blood-thinning medications may cause increased bleeding and/or bruising in the treated area.
- Tell your doctor if you have a history of cold sores (**herpes**). Any injection, including RHA® Dynamic Volume, in the general area, may trigger a recurrence of your cold sores (**herpes**).
- Tell your doctor if you have an injury or other skin condition near the injection site(s). Injection of a **dermal filler** in this situation may lead to a worsening of your condition or infection. You may have to wait until you are completely healed before using RHA® Dynamic Volume.
- Tell your doctor if you have ever developed a thick tough scar (**keloid**) or had problems with skin discoloration. It is possible that injection of any **dermal filler**, including RHA® Dynamic Volume, may make the skin thicker and change color.
- Tell your doctor if you have a history of **pigmentation disorders**. The safety of RHA® Dynamic Volume in patients with history of **pigmentation disorders** has not been studied. Use in these patients may result in changes in pigmentation.
- Tell your doctor if you have already been injected with **dermal fillers** in the same area as the one(s) you are about to be treated for. This information helps your doctor decide when and whether you should get treatment with RHA® Dynamic Volume.
- Tell your doctor if you have recently had (within 6 months), or are considering, laser treatment, chemical peeling, or any other facial procedure. Use of RHA® Dynamic Volume with these skin treatments may lead to an increased severity of the **Common Treatment Reactions** such as redness, swelling, heat, or pain in the area.
- You should not take Vitamin E, aspirin, or **anti-inflammatories** during the week prior to the injection. Taking these medications can thin your blood and may result in increased bleeding and/or more bruising in the treated area.

If you have any additional questions about any topic in this section, please discuss further with your doctor.

5. HOW WAS RHA® DYNAMIC VOLUME STUDIED?

RHA® Dynamic Volume is part of the TEOXANE **dermal fillers** RHA® Mepi family and is strictly identical to RHA® 4, except for the small amount of **anesthetic** medicine they contain.

Indeed, RHA® Dynamic Volume contains **mepivacaine** and RHA® 4 contains **lidocaine**. **Mepivacaine** and **lidocaine** are two **anesthetic** agents of the same family with the mechanism of effect. RHA® 4 and RHA® Dynamic Volume are injected in the same location, the lines from your nose to the corners of your mouth. The long-term safety and effectiveness of RHA® Dynamic Volume were evaluated in a clinical study using RHA® 4.

RHA® 4 is part of the TEOXANE **dermal filler** RHA® family and is also available in the United States to treat facial wrinkles and folds.

RHA® 4 was tested in a long-term clinical study to make sure it worked as intended, and was safe to use. The study assessed how well RHA® 4 performed when compared to another **dermal filler** already available in the United States. The study looked at how RHA® 4 smoothed away wrinkles and folds in the moving (**dynamic**) area of the face, from the nose to the corners of the mouth (**nasolabial folds**).

The first study using RHA® 4 lasted 64 weeks (15 months) and involved 120 patients. The wrinkles to be treated were considered to be moderate or severe, based on their depth. The patients were injected with RHA® 4 on one side of their face and with the other **dermal filler** on the other side. Study patients were mostly females, with light to very dark skin color. The majority of patients had light to medium skin tone. The study took place at 5 different locations across the United States.

Two weeks after the initial injection, the study patients were examined by their doctor. If their doctor felt it was necessary, he/she injected more RHA® 4 (**touch-up**) to get the desired result.

Study patients kept a diary for 14 days after each injection to record **Common Treatment Reactions** at the injection site. These diaries were then shared with their doctor.

Each patient saw their doctor at regular intervals for 12 to 15 months after the procedure. All subjects were followed for an additional 4 weeks if they had received repeated treatment at the end of the study. At each visit, the doctor measured the effects of the treatments and checked the patient to evaluate any potential problem. Each patient was also examined by a doctor who did not know which side of their face was injected with RHA® 4. This allowed the new doctor to objectively assess changes in how the patient looked compared to before the first injection.

Patients also evaluated themselves for changes in the appearance of their wrinkles and folds. They looked at themselves in a mirror and compared how they looked now against their picture taken before the first injection. They rated their results from "much improved" to "much worse" (the scale included the following grades: 1-Much improved – 2-Improved – 3-No change – 4-Worse – 5-Much worse).

Patients reported their level of pain during and after injection using a scale from 0 to 100, with "0" meaning "no pain" and "100" meaning "the worst pain possible". The pain was the most at the time of injection and was on average 23 out of 100. Five minutes after injection, the pain was on average 6 out of 100.

Finally, to evaluate how well the RHA® Mepi family (including RHA® Dynamic Volume) containing **mepivacaine** reduces discomfort (i.e, the level of pain) during injection, the RHA®-M family (specifically RHA® Dynamic Volume) was studied in a clinical study. The pain following the injection of RHA® Mepi **dermal filler** which contains **mepivacaine** was compared to the pain following the same RHA® **dermal filler** which contains **lidocaine**.

This study lasted 1 month and involved 30 patients. The patients were injected in the **nasolabial folds** with RHA® Mepi on one side of their face and with RHA® on the other side. The wrinkles to be treated were considered to be moderate or severe, based on their depth. Study patients were mostly females, with light to very dark skin color. The majority of patients had light to medium skin tone. The study took place at 3 different locations across the United States.

During and after the injection, patients reported their level of pain using a scale from 0 to 100, with "0" meaning "no pain" and "100" meaning "the worst pain possible" for each treated side of their face. The pain felt on the side treated with RHA® Mepi was almost identical to the pain in the area treated with RHA®. The pain felt was the most at the time of injection and was in between 16 and 17 on average out of 100 on both sides.

Fifteen minutes after injection, the pain was on average 5 out of 100 and was almost totally gone on both sides of the face after one hour.

In addition, study patients kept a diary for 30 days after each injection to record **Common Treatment Reactions** at the injection site. These diaries were then shared with their doctor at their next visit one month after their injection.

During this visit, one month after the initial injection, the study patients were re-examined by their doctor. The doctor measured the effects of the treatments and checked the patient to make sure there were no problems.

The patients also evaluated themselves for changes in the appearance of their wrinkles and folds. They looked at themselves in a mirror and compared how they looked now against their picture taken before the first injection. They rated their results from improved to worse: 100% of the subjects reported having their NLFs treated improved or very much improved, with the same effectiveness for both RHA® and RHA® Mepi in filling the wrinkles.

The results of the long duration study with RHA® 4 are applicable to RHA® Dynamic Volume.

6. BENEFITS

What are the expected benefits of RHA® Dynamic Volume?

The benefits expected from RHA® Dynamic Volume are identical to those expected for RHA® 4 because the two devices are the same except for the difference in anesthetic, which would not be expected to result in a difference in the overall safety and effectiveness of RHA® Dynamic Volume when compared to RHA® 4.

RHA® Dynamic Volume smooths wrinkles and folds in moving (**dynamic**) areas of the face, between the nose and the corners of the mouth (**nasolabial folds**).

In the long-term study of RHA® 4, 77 patients were evaluated at 12 months and 65 patients were evaluated at 15 months. The evaluation was based on the depth of their wrinkles. In the clinical study, RHA® 4 was shown to last 12 months in 87% of patients (67 out of 77 patients). At the end of the study, 15 months, RHA® 4 was shown to last in 89% of patients (58 out of 65 patients).

At each office visit, a doctor who did not know which side of their face had RHA® 4 injected, examined the patient. He/she evaluated the changes in the appearance of the treated wrinkles compared to their appearance in the patient's picture taken before the treatment. These doctors reported that 84% of the patients (65 out of 77 patients) showed improvement at 12 months and 80% at 15 months (52 out of 65 patients).

At each office visit, study patients were asked whether their appearance had improved or gotten worse.

The patient compared the appearance of his/her treated wrinkles against their picture taken before the first injection. More than 87% of the patients reported that their wrinkles and folds were improved at both 12 and 15 months (end of the study) after the first injection. One-month post-injection, effectiveness between RHA® 4 and RHA® Dynamic Volume was identical, supporting that RHA® Dynamic Volume is expected to exhibit the same long-term effectiveness as RHA® 4.

7. RISKS

What were the Common Treatment Reactions seen in the clinical study?

Because **mepivacaine** and **lidocaine** are two **anesthetic** medicines from the same family, it was demonstrated during the short-term clinical study that the safety profiles of the **dermal fillers** RHA®4 or RHA® Dynamic Volume were not impacted by the nature of the anesthetic agent incorporated in the **dermal filler**. RHA® 4 and RHA® Dynamic Volume have the same safety profile with identical **Common Treatment Reactions**.

In the clinical study with RHA® Dynamic Volume, most patients (97% or 29 out of 30 patients) experienced a **Common Treatment Reaction** following their injection. Some patients experienced more than one. The expected reactions at the injection site are:

- Bruising
- Firmness
- Swelling
- Pain
- Tenderness
- Redness
- Lumps/bumps
- Change of skin color
- Itching

The duration of the **Common Treatment Reactions** varied. The majority (93% or 150 of the 162 reactions) of the **Common Treatment Reactions** were gone by 14 days after injection. Of the **Common Treatment Reactions** that lasted more than 14 days, 5 events were still present on the last day of the diary (30 days after injection): 3 were firmness, 1 was itching, and 1 was lumps and bumps. They were all mild on the last day of the diary.

For most of these reactions, patients reported that they were mild or moderate (95% or 154 of the 162 reactions). This means that the patient had little to no discomfort and their daily life was not affected. They may have used medication and/or make-up.

Table 1 gives the percentage of study patients who experienced each **Common Treatment Reaction** following the injection of RHA® Dynamic Volume.

*Table 1: **Common Treatment Reactions** observed in the RHA® Dynamic Volume clinical study*

Common Treatment Reactions	Study patients who reported the Common Treatment Reaction
Tenderness	80% (24 out of 30 patients)
Firmness	80% (24 out of 30 patients)

Lumps/Bumps	73% (22 out of 30 patients)
Redness	70% (21 out of 30 patients)
Swelling	70% (21 out of 30 patients)
Bruising	63% (19 out of 30 patients)
Pain*	40% (12 out of 30 patients)
Change in skin color	37% (11 out of 30 patients)
Itching	23% (7 out of 30 patients)

*pain was reported in the days following the injection, which corresponds to the time after the anesthetic effect dissipated

What other possible reactions could occur?

Other possible reactions can occur after the injection of a **dermal filler** such as RHA® Dynamic Volume, although they were not observed in the clinical study. Possible reactions may be:

- Infection – Any time a **dermal filler** is injected under the skin there is a risk of infection at the site of injection. It may create hard and swollen lumps that may contain pus. Infection may require antibiotic treatment or other medical intervention.
- Granuloma – Red raised lumps that may appear weeks or months after injection. They may need to be treated by a doctor to make them go away. It may require additional procedures.
- Acne-like rashes – If you have a sensitive skin, the injection of a **dermal filler** may create irritation or rash at the site of the treatment that can be compared to acne.
- Displacement of the gel - It is possible the injected gel may move out of the desired treatment area. Your appearance may be affected.
- Blisters – Any injection, including with RHA® Dynamic Volume, may lead to the formation of blisters at the point of injection.
- Scars – With any type of injection, including with RHA® Dynamic Volume, scarring may occur.
- **Keloid** – Keloid scarring, a thick tough scar that grows beyond the borders of the original wound, may occur from **dermal filler** injection.
- Scab - The injection of a **dermal filler**, such as RHA® Dynamic Volume, may result in the skin becoming dry and crusty.
- Skin peeling (shedding) – The skin may dry as a reaction to the cleansing agent. The dry skin may be stressed with the injection and result in peeling or shedding.

You should contact your doctor if you experience any of these reactions or if you notice anything unusual at the site of the treatment. Most of these reactions go away within a few days on their own but some may persist for more than 30 days. Your doctor may choose to treat them with medications.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Other serious reactions may occur following the injection of **dermal fillers** to smooth wrinkles. Contact your doctor immediately if any of these happen:

- One of the risks with using this product is unintentional injection into a blood vessel. The chances of this happening are very small, but if it does happen, the complications can be serious and may be permanent. These complications, which have been reported for facial injections, can include vision abnormalities, blindness, stroke, temporary scabs, or permanent scarring of the skin. If you have changes in your vision, signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance of the skin, or unusual pain during or shortly after treatment, you should notify your health care practitioner immediately.
- Severe allergic reactions (anaphylaxis) - An **allergic reaction** to a material used to make a **dermal filler** that could occur shortly after the injection. Symptoms could include a rash, sneezing, itching, congestion, or difficulty breathing.

You should discuss the potential treatment risks and benefits with your doctor before the injection.

8. PROCEDURE

What happens in the doctor's office before the treatment?

Note that each doctor may have their own process for treating patients.

Before the injection procedure, your doctor will ask you questions about your medical history. He/she will ask about your treatment goals. Your doctor will discuss whether you are a good candidate for RHA® 4 Dynamic Volume. He/she will review with you what to expect during and after treatment, including possible risks.

During this discussion, it is very important to tell your doctor about:

- all medications you are taking, both over the counter and prescription
- any previous facial treatment you may have received
- and any health conditions for which you are receiving medical attention

Your doctor will also examine your skin in and around the treatment area and may take photos. The treatment area will be cleaned and prepared with a cleansing agent. Your doctor may use a pen to mark your face in the planned areas of injection.

Do the injections hurt?

Injections may cause some pain during and after the procedure. Your doctor will discuss different options for pain management with you. RHA® Dynamic Volume contains an **anesthetic** medicine (**mepivacaine**) to help reduce injection site pain. This pain is temporary and usually lessens within a few minutes. To prevent or reduce pain from the injection, your doctor may use ice packs, or another **anesthetic**, both before and after the injection.

What happens during the treatment?

RHA® Dynamic Volume is slowly injected into the facial skin in small amounts until your doctor sees the desired result which creates a more youthful appearance of the face. For most patients, the procedure only takes 15-30 minutes.

Once your doctor has finished injecting the treatment area, he/she may gently massage your face to help smooth and distribute the gel evenly.

Your doctor may also apply an ice pack to help decrease swelling and pain.

The amount of RHA® Dynamic Volume used depends on the depth of your wrinkles and your treatment goals. The right amount to be injected will be decided by your doctor during the procedure. Injection of additional RHA® Dynamic Volume (**touch-up** treatment) may be needed 2 to 4 weeks after the initial treatment to achieve the desired aesthetic outcome. In the long-term clinical study with RHA® 4, 27% of the patients received a **touch-up** treatment 2 weeks after initial treatment to achieve their desired results. Your doctor will decide how much RHA® Dynamic Volume is needed for the **touch-up** treatment.

What happens after the treatment?

Your doctor may advise you to apply cold compresses to the treated area to help reduce pain and swelling. In order to prevent injury, ask your doctor how long you can leave ice packs on the treated area.

Be aware that numbness, short-term loss of touch or feeling, and tingling around the injection area may occur due to the numbing medicine (**anesthetic**). It usually goes away within a few hours. Due to this numbness, you may not have a normal feeling of hot or cold in this area.

Ask your doctor about any limits for exercising and exposure to sun, cold, or heat (sauna, steam room). Exposure to any of these for the first 24 hours may increase short-term redness, swelling, and/or itching at the injection site.

You should ask your doctor when make-up may be applied after your treatment. Using make-up too soon may increase the risk of infection or change in skin color.

Most **Common Treatment Reactions** like bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change of skin color, and itching go away on their own within a few days, but your doctor may choose to treat them with medications. Refer to section 7, RISKS.

When should I call my doctor?

Call your doctor if you have any questions or concerns after your procedure.

Call your doctor immediately if you have:

- Signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion)
- Changes in your vision
- Pain which increases after your treatment
- Significant pain away from the injection site
- Significant whitening or darkening of the skin
- Any treatment reaction other than bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, itching, which occurs in the first two weeks
- Any treatment reaction in the treated area, including a lump or hardening under the skin, that appears weeks or months after your injection.

The following are common reactions often seen after treatment with **dermal fillers**. They usually go away within 2 weeks. If you are concerned, or if they last more than 2 weeks, call your doctor:

- Bruising
- Firmness
- Swelling

- Pain
- Tenderness
- Redness
- Lumps/bumps
- Change in skin color
- Itching

9. ADDITIONAL INFORMATION

In case you have any further questions, please contact Revance Therapeutics, Inc. at 877-3REV-NOW (877-373-8669).

www.revance.com

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RHA® Dynamic Volume for Cheek fullness

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1. GLOSSARY

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Allergic reaction: allergic reactions occur when a person's immune system (needed to fight infections) overreacts to substances that are harmless for most people. Symptoms could include a rash, sneezing, itching, congestion, or difficulty breathing

Anaphylaxis: a severe **allergic reaction** that needs medical treatment right away

Anesthetic: a medication that reduces pain; it can be added to a cream or a **dermal filler**; sometimes called a numbing medicine

Anticoagulants: medications that thin your blood

Anti-inflammatory: a medicine that reduces pain, heat, redness, and swelling, which are symptoms of inflammation

BDDE: 1,4-butanediol diglycidyl ether, a chemical compound used in very small amount to bind the chains of **HA** together to form a gel

Cannula: a thin metal tube with a blunt tip. It may be used as an alternative to needles for injections

Cheeks: area of injection as illustrated in Figure 1

Common Treatment Reaction: reactions that can be expected after injection of a **dermal filler**. It includes bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change in skin color, and itching

Dermal filler: material that is injected under the skin to help smooth and plump the **cheeks**

Dynamic: able to move, not fixed in place, such as the skin on the face

Granuloma: localized hardening under the skin, like a lump, appearing weeks or months after the injection

Herpes: a virus that causes certain skin conditions, such as cold sores

Hyaluronic Acid (HA): a naturally occurring substance found in the human body which helps maintain skin structure and feel. The HA found in RHA® Dynamic Volume is a different form than the HA found in the human body

Immunosuppressive therapy: medications that reduce the body's normal response to infections, allergens, anything not normally found in the body.

Keloid: a thick tough scar.

Lidocaine: a type of **anesthetic** medication that helps reduce pain during injection. The anesthetic medication temporarily (less than 24 hours) anesthetizes the treatment area.

Mepivacaine: a type of **anesthetic** medication that helps reduce pain during injection. The anesthetic medication temporarily (less than 24 hours) anesthetizes the treatment area.

Nasolabial folds (NLFs): the medical term for the wrinkles and fold lines between the nose and the corners of the mouth

Pigmentation disorders: general term to refer to health conditions that affect the color of the skin

Severe common treatment reaction: reaction following an injection with symptoms that caused severe discomfort, compromised the performance of daily activities and for which treatment of the symptoms was needed. The severity is determined by the patient

Streptococcus equi: a bacteria, which does not cause illness in people, used to make the **hyaluronic acid**

Therapy: treatment intended to reduce, heal or cure pain, disease, or physical reaction

Touch-up: an additional injection, performed 2 to 4 weeks after the initial injection. Some patients may require a touch-up treatment to achieve the desired aesthetic results

Treatment Related Adverse Events (TRAEs): any unusual medical occurrence in a subject following the injection which is related to the dermal filler as determined by the doctor. It may be any symptoms, disease or reaction associated with the use of the dermal filler

2. PRODUCT DESCRIPTION

What is RHA® Dynamic Volume?

RHA® Dynamic Volume is an injectable gel (also called a **dermal filler**) used to augment volume of the **cheeks** to correct age-related volume deficiencies. It is injected into the **cheek**, a moving (**dynamic**) area (see Figure 1). It is approved for use in adults over 22 years of age.

RHA® Dynamic Volume is produced with **hyaluronic acid (HA)** and using an advanced technology to obtain a soft and long-lasting injectable gel to increase **cheek** volume. Chains of **HA** are linked together through a chemical reaction triggered by a small quantity of **BDDE** to create the gel texture of RHA® Dynamic Volume. The **HA** of the gel is made from a non-animal source.

RHA® Dynamic Volume contains a small amount of an **anesthetic** medicine (**mepivacaine**), to help reduce discomfort during injection. The effect of the anesthetic is temporary, some discomfort may be experienced due to the injection of the filler during and after the procedure.

Hyaluronic acid (HA) is a naturally occurring substance found in the human body. Your body's own **HA** helps maintain the skin's structure and its natural feel.

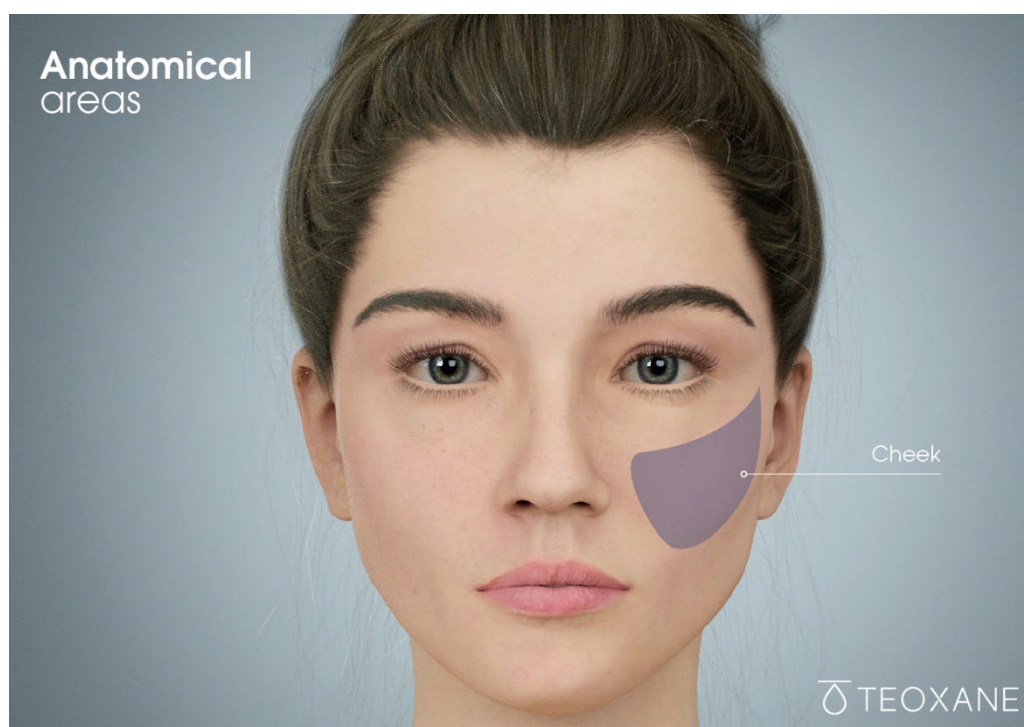


Figure 1: Location of **cheek** area

How does it work?

RHA® Dynamic Volume is injected into the skin with an ultrafine needle or a small, blunt-tipped **cannula** to add volume to the **cheek** area and creates a more defined contour and a younger-looking face. This volumizing effect has been shown to last 6 months in 79% of the patients (103 out of 130 patients) and lasted 12 months in 66% of the patients (84 out of 128 patients).

RHA® Dynamic Volume is not a permanent gel. It slowly goes away as the body absorbs the gel. The volumizing effect will gradually disappear.

3. CONTRAINDICATIONS

Are there any reasons why I should not receive RHA® Dynamic Volume?

Your doctor will ask about your medical history to see if RHA® Dynamic Volume is right for you. You should not use RHA® Dynamic Volume if you have a history of:

- severe **allergic reactions (anaphylaxis)** or history or presence of multiple severe allergies: an injection of RHA® Dynamic Volume may result in an **allergic reaction**.
- **allergic reactions** to the material (from ***Streptococcus equi***) used to make the **HA** in RHA® Dynamic Volume: an injection of RHA® Dynamic Volume may result in an **allergic reaction**.
- **allergic reactions** to **mepivacaine** or other similar substances such as lidocaine used to reduce pain: an injection of RHA® Dynamic Volume may result in an **allergic reaction**.
- **bleeding disorders**: any injection, including RHA® Dynamic Volume and other **dermal fillers**, may result in a higher risk of bruising or bleeding in the treated area.

4. PRECAUTIONS

Are there precautions that I should discuss with my doctor?

The following are important treatment considerations that you should discuss with your doctor. These hazards, if not avoided, could result in unsatisfactory results or complications.

- Tell your doctor if you are under 22 years of age. RHA® Dynamic Volume has not been studied in people younger than 22 and the effects are not known.
- Tell your doctor if you are pregnant (or plan to be) or breastfeeding. RHA® Dynamic Volume has not been studied in women who were pregnant or breastfeeding and the effects are not known.
- Tell your doctor if you are taking medicine that reduces your body's ability to fight infection (**immunosuppressive therapy**). Taking this type of medicine may increase the risk of infection following the injection of RHA® Dynamic Volume or other **dermal fillers**.
- Be sure to tell your injecting doctor if you are using "blood thinners" (**anticoagulants**) or any other medications that affect bleeding. Do not stop taking them until you speak with the doctor who prescribed them for you. Tell your prescribing doctor that you are considering having your **cheeks** treated with RHA® Dynamic Volume. These blood-thinning medications may cause increased bleeding and/or bruising in the treated area.
- Tell your doctor if you have a history of cold sores (**herpes**). Any injection, including RHA® Dynamic Volume, in the general area, may trigger a recurrence of your cold sores (**herpes**).
- Tell your doctor if you have an injury or other skin condition near the injection site(s). Injection of a **dermal filler** in this situation may lead to a worsening of your condition or infection. You may have to wait until you are completely healed before using RHA® Dynamic Volume.
- Tell your doctor if you have ever developed a thick tough scar (**keloid**) or had problems with skin discoloration. It is possible that injection of any **dermal filler**, including RHA® Dynamic Volume, may make the skin thicker and change color. However, when RHA® Dynamic Volume was studied in patients with different skin tones (pale to dark), there were no reports of this happening.
- Tell your doctor if you have a history of **pigmentation disorders**. The safety of RHA® Dynamic Volume in patients with history of **pigmentation disorders** has not been studied. Use in these patients may result in changes in pigmentation.
- Tell your doctor if you have already been injected with **dermal fillers** in the same area as the one(s) you are about to be treated for. This information helps your doctor decide when and whether you should get treatment with RHA® Dynamic Volume.

- Tell your doctor if you have recently had (within 6 months), or are considering, laser treatment, chemical peeling, or any other facial procedure. Use of RHA® Dynamic Volume with these skin treatments may lead to an increased severity of the **Common Treatment Reactions** such as redness, swelling, heat, or pain in the area.
- You should not take Vitamin E, aspirin, or **anti-inflammatories** during the week prior to the injection. Taking these medications can thin your blood and may result in increased bleeding and/or more bruising in the treated area.

If you have any additional questions about any topic in this section, please discuss further with your doctor.

5. HOW WAS RHA® DYNAMIC VOLUME STUDIED?

RHA® Dynamic Volume is part of the TEOXANE **dermal fillers** RHA® Mepi family and is strictly identical to RHA® 4, except for the small amount of **anesthetic** medicine they contain.

Indeed, RHA® Dynamic Volume contains **mepivacaine** and RHA® 4 contains **lidocaine**. **Mepivacaine** and **lidocaine** are two **anesthetic** agents of the same family with the same mechanism of effect. RHA® 4 and RHA® Dynamic Volume are injected in the same location, the **cheek** area. The long-term safety and effectiveness of RHA® Dynamic Volume were evaluated in a clinical study using RHA® 4.

RHA® 4 was tested in a clinical study to make sure it worked as intended and was safe to use. The study was conducted to test the effectiveness and safety of RHA® 4 in improving **cheek** fullness. This study lasted 52 weeks (12 months) and involved 201 patients. The patients who were treated presented with moderate or severe volume loss of their **cheeks**, based on their fullness. They were injected with either RHA® 4 or with another dermal filler used as a control. Study patients were mostly females, with light to very dark skin color. The study took place at 8 different locations across the United States.

Four weeks after the initial injection, the study patients were examined by their doctor. If their doctor felt it was necessary, **touch-up** injections were given as needed with the same product as used at the initial treatment to get the desired result.

Study patients kept a diary for 30 days after each injection to record **common treatment reactions** at the injection site. These diaries were then shared with their doctor.

Each patient saw their doctor at regular intervals for 52 weeks after the procedure. All subjects were followed for an additional 12 weeks if they had received repeated treatment at the end of the study. At each visit, the doctor measured the effects of the treatments and checked the patient to make sure there were no problems. Each patient was also examined by a doctor who did not know which product was injected. This allowed the new doctor to objectively assess changes in how the patient looked compared to before the first injection, without knowing which product was injected.

Patients also evaluated themselves for changes in the appearance of their **cheeks**. They looked at themselves in a mirror and compared how they looked now against their own picture taken before the first injection. They rated their results from “much improved” to “much worse” (the scale included the following grades: 1-Much improved – 2-Improved – 3-No change – 4-Worse – 5-Much worse). Patients also assessed how satisfied they were with their **cheeks** at rest and when smiling (symmetry, smoothness, attractiveness, contour and youthful fullness). Patients reported their level of pain during and after injection using a scale from 0 to 100, with “0” meaning “no pain” and “100” meaning “the worst pain possible”. The pain was the most at the time of injection and was on average 7 out of 100. Five minutes after injection, the pain was on average 3 out of 100.

The results of the clinical study with RHA® 4 are applicable to RHA® 4 Dynamic Volume.

6. BENEFITS

What are the expected benefits of RHA® Dynamic Volume?

The benefits expected from RHA® Dynamic Volume are identical to those expected for RHA® 4 because the two devices are the same except for the difference in anesthetic, which would not be expected to result in a difference in the overall safety and effectiveness of RHA® Dynamic Volume when compared to RHA® 4.

RHA® 4 will temporally add volume to your **cheeks**. At 8 weeks, 137 patients were evaluated and at 52 weeks (1 year), 128 patients were evaluated. The evaluation was based on the fullness of their **cheeks**. In the clinical study, RHA® 4 had a visible effect in 88% of patients (120 out of 137 patients) at 8 weeks. At the end of the study, 52 weeks (1 year), RHA® 4 still had a visible effect in 66% of patients (84 out of 128 patients).

At each office visit, a doctor who did not know which product was injected (RHA® 4 or the other product), examined the patient. They evaluated the changes in volume of the treated **cheeks** compared to their appearance in the patient's picture taken before the treatment. These doctors reported that 94% of the patients (129 out of 137 patients) showed improvement at 8 weeks, 76% (97 out of 128 patients) at 52 weeks. At each office visit, study patients were asked whether their appearance had improved or worsened. The patient compared the fullness of their treated **cheeks** against their own picture taken before the first injection. 96% of the patients reported that their **cheeks** were improved at 8 weeks. More than 81% of the patients reported that their **cheeks** were improved at 52 weeks (end of study) after the last injection (initial injection or touch-up).

At each study visit, patients completed satisfaction questionnaires, about the satisfaction with their **cheeks**, at rest and when smiling. Patients reported very high satisfaction score with their **cheeks** at both rest and when smiling through 1 year.

Finally, over 95% of patients thought their **cheeks** looked natural 1 year after treatment.

7. RISKS

What were the Common Treatment Reactions seen in the clinical study?

Because **mepivacaine** and **lidocaine** are two **anesthetic** medicines from the same family, it was demonstrated during a clinical study that the safety profiles of the **dermal fillers** RHA®4 or RHA® Dynamic Volume were not impacted by the nature of the anesthetic agent incorporated in the **dermal filler**. RHA® 4 and RHA® Dynamic Volume have the same safety profile with identical **Common Treatment Reactions**.

In the clinical study with RHA®4 into the **cheeks**, most patients (91%, 128 out of 141 patients) experienced a **common treatment reaction** following their injection. Some patients experienced more than one. The expected reactions at the injection site are:

- Bruising
- Firmness
- Swelling
- Pain
- Tenderness

- Redness
- Lumps/bumps
- Change of skin color
- Itching

The duration of the **common treatment reactions** varied. The majority (68%, 87 of the 128 patients) of patients had their **common treatment reactions** resolved 14 days after injection. Of those **common treatment reactions** which lasted for 30 days or more occurring in 13% of the patients, 18 of the 128 patients), the most frequent were lumps/bump and firmness at site of injection.

For most of these reactions, patients reported that they were mild or moderate (95%, 121 of the 128 reactions). This means that the patient had little to no discomfort and their daily life was not affected. They may have used medication and/or make-up. Of the **common treatment reactions** that were reported as severe by the patients (5%, 7 of the 128 reactions), the most frequent were firmness. After 30 days, all the **common treatment reactions** were mild.

Table 1 gives the percentage of study patients who experienced each common treatment reaction following the injection.

*Table 1: **Common treatment reactions** observed in the clinical study*

Common Treatment Reactions	Study patients who reported the common treatment reaction
Tenderness	80% (113 out of 141 patients)
Skin firmness	77% (108 out of 141 patients)
Swelling	69% (98 out of 141 patients)
Lumps/Bumps	55% (77 out of 141 patients)
Bruising	52% (74 out of 141 patients)
Pain	50% (70 out of 141 patients)
Redness	43% (61 out of 141 patients)
Change in skin color	23% (32 out of 141 patients)
Itching	12% (17 out of 141 patients)

When **common treatment reactions** lasted longer than the 30 days of the diary or if treatment reactions were not considered typical in type and/or duration and/or severity, they were called **Treatment-Related Adverse Events (TRAEs)**. All **Treatment-Related Adverse Events** were mild or moderate. No severe Treatment-Related Adverse Events were observed. The vast majority of **Treatment-Related Adverse Events** (82%) resolved within 14 days, four events lasted between 30 and 90 days and 1 event lasted 227 days.

All **Treatment-Related Adverse Events** eventually resolved without consequence.

What other possible reactions could occur?

Other possible reactions can occur after the injection of a **dermal filler** such as RHA® Dynamic Volume, although they were not observed in the clinical study. Possible reactions may be:

- Infection – Any time a **dermal filler** is injected under the skin there is a risk of infection at the site of injection. It may create hard and swollen lumps that may contain pus. Infection may require antibiotic treatment or other medical intervention.

- **Granuloma** – Red raised lumps that may appear weeks or months after injection. They may need to be treated by a doctor to make them go away. It may require additional procedures.
- Acne-like rashes – If you have a sensitive skin, the injection of a **dermal filler** may create irritation or rash at the site of the treatment that can be compared to acne.
- Displacement of the gel - It is possible the injected gel may move out of the desired treatment area. Your appearance may be affected.
- Blisters – Any injection, including with RHA® Dynamic Volume, may lead to the formation of blisters at the point of injection.
- Scars – With any type of injection, including with RHA® Dynamic Volume, scarring may occur.
- Scab - The injection of a **dermal filler**, such as RHA® Dynamic Volume, may result in the skin becoming dry and crusty.

Other less reported adverse reactions with RHA®4 product may occur such as edema, skin peeling (dry skin and shedding), inflammatory reaction, abscess (a painful swollen area on or in the body that contains pus (= thick, yellow liquid)), overcorrection, skin necrosis, urticaria, angioedema (swelling in the deep layers of the skin), chapped lips (dry, cracked or sore lips), dermatitis (skin red and painful), fibrosis (excessive tissue growth), herpes breakout (recurrence of cold sore), localized numbness, pustules (a small raised area on the skin that contains pus), telangiectasia (transient dilation of blood vessels at injection site inducing a network-like aspect on the skin).

You should contact your doctor if you experience any of these reactions or if you notice anything unusual at the site of the treatment. Most of these reactions go away within a few days on their own but some may persist for more than 30 days. Your doctor may choose to treat them with medications.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Other serious reactions may occur following the injection of **dermal fillers** to smooth wrinkles. Contact your doctor immediately if any of these happen:

- One of the risks with using this product is unintentional injection into a blood vessel. The chances of this happening are very small, but if it does happen, the complications can be serious and may be permanent. These complications, which have been reported for facial injections, can include vision abnormalities, blindness, stroke, temporary scabs, or permanent scarring of the skin. If you have changes in your vision, signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance of the skin, or unusual pain during or shortly after treatment, you should notify your health care practitioner immediately.
- Non-severe and severe allergic reactions (anaphylaxis) - An **allergic reaction** to a material used to make a **dermal filler** that could occur shortly after the injection. Symptoms could include a rash, sneezing, itching, congestion, or difficulty breathing.

You should discuss the potential treatment risks and benefits with your doctor before the injection.

8. PROCEDURE

What happens in the doctor's office before the treatment?

Note that each doctor may have their own process for treating patients.

Before the injection procedure, your doctor will ask you questions about your medical history. He/she will ask about your treatment goals. Your doctor will discuss whether you are a good candidate for RHA® Dynamic Volume. He/she will review with you what to expect during and after treatment, including possible risks.

During this discussion, it is very important to tell your doctor about:

- all medications you are taking, both over the counter and prescription
- any previous facial treatment you may have received
- and any health conditions for which you are receiving medical attention

Your doctor will also examine your skin in and around the treatment area and may take photos. The treatment area will be cleaned and prepared with a cleansing agent. Your doctor may use a pen to mark your face in the planned areas of injection.

Do the injections hurt?

Injections may cause some pain during and after the procedure. Your doctor will discuss different options for pain management with you. RHA® Dynamic Volume contains an **anesthetic** medicine (**mepivacaine**) to help reduce injection site pain. This pain is temporary and usually lessens within a few minutes. To prevent or reduce pain from the injection, your doctor may use ice packs, or another **anesthetic**, both before and after the injection.

What happens during the treatment?

RHA® Dynamic Volume is slowly injected into the **cheeks** in small amounts until your doctor sees the desired result is to increase your **cheek** volume. For most patients, the procedure only takes 15-30 minutes.

Once your doctor has finished injecting the treatment area, he/she may gently massage your face to help smooth and distribute the gel evenly.

Your doctor may also apply an ice pack to help decrease swelling and pain.

The amount of RHA® Dynamic Volume used depends on the volume loss of your **cheeks** and your treatment goals. The right amount to be injected will be decided by your doctor during the procedure. Injection of additional RHA® Dynamic Volume (**touch-up** treatment) may be needed 2 to 4 weeks after the initial treatment to achieve the desired aesthetic outcome. In the clinical study 63% of the patients received a **touch-up** treatment 4 weeks after initial treatment to achieve their desired results. Your doctor will decide how much RHA® Dynamic Volume is needed for the **touch-up** treatment.

What happens after the treatment?

Your doctor may advise you to apply cold compresses to the treated area to help reduce pain and swelling. In order to prevent injury, ask your doctor how long you can leave ice packs on the treated area.

Be aware that numbness, short-term loss of touch or feeling, and tingling around the injection area may occur due to the numbing medicine (**anesthetic**). It usually goes away within a few hours. Due to this numbness, you may not have a normal feeling of hot or cold in this area.

Ask your doctor about any limits for exercising and exposure to sun, cold, or heat (sauna, steam room). Exposure to any of these for the first 24 hours may increase short-term redness, swelling, and/or itching at the injection site.

You should ask your doctor when make-up may be applied after your treatment. Using make-up too soon may increase the risk of infection or change in skin color.

Most **Common Treatment Reactions** like bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change of skin color, and itching go away on their own within a few days, but your doctor may choose to treat them with medications. In some rare worst cases situations, other procedures may be undertaken including incision and drainage (withdrawal of fluids from a wound, a sore) or excision (surgical removal) of the implant. Refer to section 7, RISKS.

When should I call my doctor?

Call your doctor if you have any questions or concerns after your procedure.

Call your doctor immediately if you have:

- Signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion)
- Changes in your vision
- Pain which increases after your treatment
- Significant pain away from the injection site
- Significant whitening or darkening of the skin
- Any treatment reaction other than bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, itching, which occurs in the first two weeks
- Any treatment reaction in the treated area, including a lump or hardening under the skin, that appears weeks or months after your injection.

The following are common reactions often seen after treatment with **dermal fillers**. They usually go away within 2 weeks. If you are concerned, or if they last more than 2 weeks, call your doctor:

- Bruising
- Firmness
- Swelling
- Pain
- Tenderness
- Redness
- Lumps/bumps
- Change in skin color
- Itching

9. ADDITIONAL INFORMATION

In case you have any further questions, please contact Revance Therapeutics, Inc. at 877-3REV-NOW (877-373-8669).

www.revance.com

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RHA®4 for Nasolabial Folds correction

Patient Information Brochure

Please read this document carefully before your treatment, it contains important information about RHA®4.

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1. GLOSSARY

Note: the terms in the glossary are **bold** throughout the document.

Allergic reaction: allergic reactions occur when a person's immune system (needed to fight infections) overreacts to substances that are harmless for most people. Symptoms could include a rash, sneezing, itching, congestion or difficulty breathing

Anaphylaxis: a severe **allergic reaction** which needs medical treatment right away

Anesthetic: a medication that reduces pain; it can be added to a cream or a **dermal filler**; sometimes called a numbing medicine

Anticoagulants: medications that thin your blood

Anti-inflammatory: a medicine which reduces pain, heat, redness, and swelling, which are symptoms of inflammation

BDDE: 1,4-butanediol diglycidyl ether, a chemical compound used in very small amount to bind the chains of **HA** together to form a gel

Cannula: a thin metal tube with a blunt tip. It may be used as an alternative to needles in NLF injections

Common treatment reaction: reactions which can be expected after injection of a **dermal filler**. It includes bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change in skin color, and itching

Dermal filler: material which is injected under the skin to help smooth and plump wrinkles and folds

Dynamic: able to move, not fixed in place, such as the skin on the face

Granuloma: localized hardening under the skin, like a lump, appearing weeks or months after the injection

Herpes: a virus which causes certain skin conditions, such as cold sores

Hyaluronic Acid (HA): a naturally occurring substance found in the human body which helps maintain skin structure and feel. The HA found in RHA®4 is a different form than the HA found in the human body

Immunosuppressive therapy: medications that reduce the body's normal response to infections, allergens, anything not normally found in the body

Keloid: a thick tough scar

Lidocaine: a type of **anesthetic** medication which helps reduce pain

Nasolabial folds (NLFs): the medical term for the wrinkles and fold lines between the nose and the corners of the mouth

Pigmentation disorders: general term to refer to health conditions that affect the color of the skin

Severe common treatment reaction: reaction following an injection with symptoms that caused severe discomfort, compromised the performance of daily activities and for which treatment of the symptoms was needed. The severity is determined by the patient.

Streptococcus equi: a bacteria, which does not cause illness in people, used to make the **hyaluronic acid**

Therapy: treatment intended to reduce, heal or cure pain, disease or physical reaction

Touch-up: an additional injection, performed 2 to 4 weeks after the initial injection. Some patients may require a touch-up treatment to achieve the desired aesthetic results

Treatment Related Adverse Events (TRAEs): any unusual medical occurrence in a subject following the injection which is related to the dermal filler as determined by the doctor. It may be any symptoms, disease or reaction associated with the use of the dermal filler.

2. PRODUCT DESCRIPTION

What is RHA®4?

RHA®4 is an injectable gel (also called a **dermal filler**) used to treat facial wrinkles and folds. It is injected in the moving (**dynamic**) area of the face especially between the nose and corners of the mouth (**nasolabial folds**) (see Figure 1). It is approved for use in adults over 22 years of age.

RHA®4 is produced with **hyaluronic acid (HA)**, using an advanced technology to obtain a soft and long lasting injectable gel to smooth facial wrinkles and folds. Chains of **HA** are linked together through a chemical reaction triggered by a small quantity of **BDDE** to create the gel texture of RHA®4. The **HA** of the gel is made from a non-animal source.

RHA®4 contains a small amount of an **anesthetic** medicine (**lidocaine**), to help reduce discomfort during injection. The effect of the anesthetic is temporary, some discomfort may be experienced due to the injection of the filler during and after the procedure.

Hyaluronic acid (HA) is a naturally occurring substance found in the human body. Your body's own **HA** helps maintain the skin's structure and its natural feel.

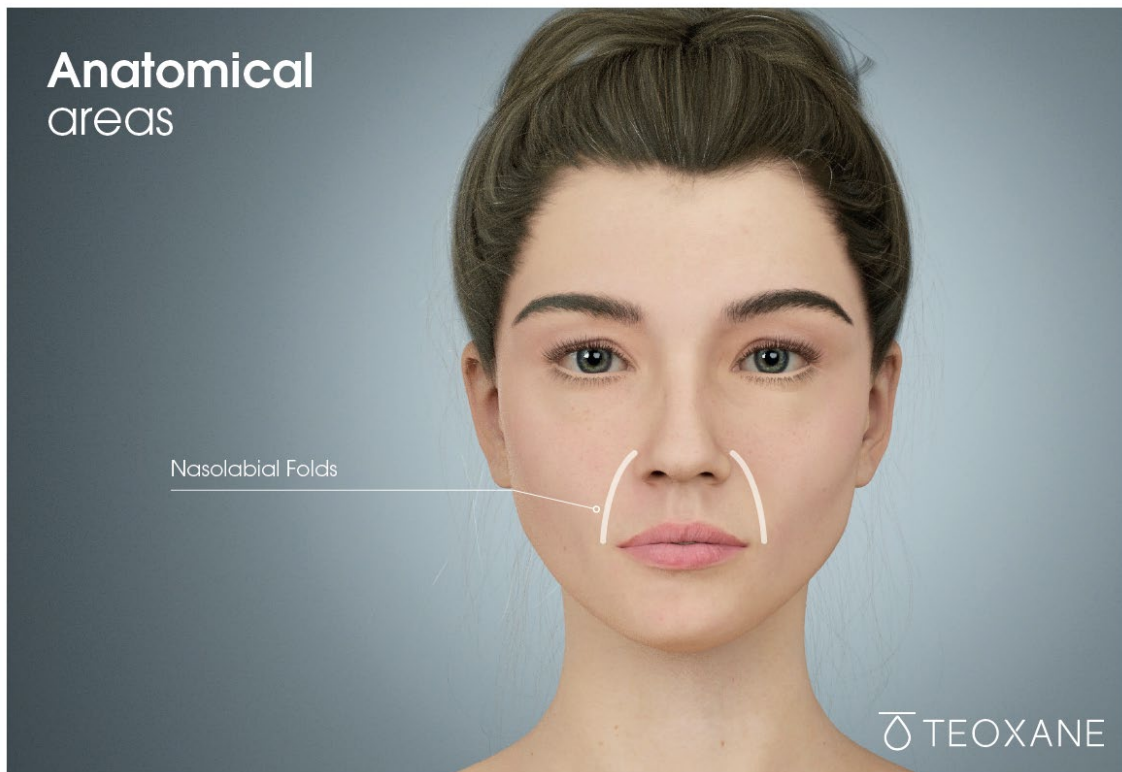


Figure 1: Location of **nasolabial folds**

How does it work?

RHA®4 is injected into the skin with an ultrafine needle or a small, blunt-tipped **cannula** to plump the skin to fill in and smooth away wrinkles and folds such as the lines from your nose to the corners of your mouth (**nasolabial folds**). This smoothing effect has been shown to last 12 months in 87% of the patients (67 out of 77 patients) and lasted 15 months in 89% of the patients (58 out of 65 patients).

RHA®4 is not a permanent gel. It slowly goes away as the body absorbs the gel. The smoothing and plumping effect will gradually disappear.

3. CONTRAINDICATIONS

Are there any reasons why I should not receive RHA®4?

Your doctor will ask about your medical history to see if RHA®4 is right for you. You should not use RHA®4 if you have a history of:

- severe **allergic reactions (anaphylaxis)** or history or presence of multiple severe allergies. An injection of RHA®4 may result in an **allergic reaction**.
- **allergic reactions** to the material (from ***Streptococcus equi***) used to make the **HA** in RHA®4. An injection of RHA®4 may result in an **allergic reaction**.
- **allergic reactions** to **lidocaine** or other similar substances used to reduce pain. An injection of RHA®4 may result in an **allergic reaction**.

- bleeding disorders. Any injection, including RHA®4 and other **dermal fillers**, may result in a higher risk of bruising or bleeding in the treated area.

4. PRECAUTIONS

Are there precautions that I should discuss with my doctor?

The following are important treatment considerations that you should discuss with your doctor. These hazards, if not avoided, could result in unsatisfactory results or complications:

- Tell your doctor if you are under 22 years of age. RHA®4 has not been studied in people younger than 22 and the effects are not known.
- Tell your doctor if you are pregnant (or plan to be) or breastfeeding. RHA®4 has not been studied in women who were pregnant or breastfeeding and the effects are not known.
- Tell your doctor if you are taking medicine that reduces your body's ability to fight infection (**immunosuppressive therapy**). Taking this type of medicine may increase the risk of infection following the injection of RHA®4 or other **dermal fillers**.
- Be sure to tell your injecting doctor if you are using "blood thinners" (**anticoagulants**), or any other medications that affect bleeding. Do not stop taking them until you speak with the doctor who prescribed them for you. Tell your prescribing doctor that you are considering having your wrinkles treated with RHA®4. These blood thinning medications may cause increased bleeding and/or bruising in the treated area.
- Tell your doctor if you have a history of cold sores (**herpes**). Any injection, including RHA®4, in the general area may trigger a recurrence of your cold sores (**herpes**).
- Tell your doctor if you have an injury, or other skin condition near the injection site(s). Injection of a **dermal filler** in this situation may lead to a worsening of your condition or infection. You may have to wait until you are completely healed before using RHA®4.
- Tell your doctor if you have ever developed a thick tough scar (**keloid**) or had problems with skin discoloration. It is possible that injection of any **dermal filler**, including RHA®4, may make the skin thicker and change color. However, when RHA®4 was studied in patients with different skin tones (pale to dark), there were no reports of this happening.
- Tell your doctor if you have a history of **pigmentation disorders**. The safety of RHA®4 in patients with history of **pigmentation disorders** has not been studied. Use in these patients may result in changes in pigmentation.
- Tell your doctor if you have already been injected with **dermal fillers** in the same area as the one(s) you are about to be treated for. This information helps your doctor decide when and whether you should get treatment with RHA®4.
- Tell your doctor if you have recently had (within 6 months), or are considering, laser treatment, chemical peeling or any other facial procedure. Use of RHA®4 with these skin treatments may lead to an increased severity of the **common treatment reactions** such as redness, swelling, heat or pain in the area.
- You should not take Vitamin E, aspirin, or **anti-inflammatories** during the week prior to the injection. Taking these medications can thin your blood and may result in increased bleeding and/or more bruising in the treated area.

If you have any additional questions about any topic in this section, please discuss further with your doctor.

5. HOW WAS RHA®4 STUDIED?

RHA®4 is part of the TEOXANE **dermal filler** RHA® family and is also available in the United States to treat facial wrinkles and folds.

RHA®4 was tested in two clinical studies to make sure it worked as intended, and was safe to use. One was with needle injections, and one was with cannula injections. These studies both assessed how well RHA®4 performed when compared to another **dermal filler** already available in the United States. The study looked at how RHA®4 smoothed away wrinkles and folds in the moving (**dynamic**) area of the face from the nose to the corners of the mouth (**nasolabial folds**).

The first study using needles lasted 64 weeks (15 months) and involved 120 patients. The wrinkles to be treated were considered to be moderate or severe, based on their depth. The patients were injected with RHA®4 on one side of their face and with the other **dermal filler** on the other side. Study patients were mostly females, with light to very dark skin color. The majority of patients had light to medium skin tone. The study took place at 5 different locations across the United States.

Two weeks after the initial injection, the study patients were examined by their doctor. If their doctor felt it was necessary, he / she injected more RHA®4 (**touch-up**) to get the desired result.

Study patients kept a diary for 14 days after each injection to record **common treatment reactions** at the injection site. These diaries were then shared with their doctor.

Each patient saw their doctor at regular intervals for 12 to 15 months after the procedure. All subjects were followed for an additional 4 weeks if they had received repeated treatment at the end of the study. At each visit, the doctor measured the effects of the treatments and checked the patient to evaluate any potential problem.

Each patient was also examined by a doctor who did not know which side of their face was injected with RHA®4. This allowed the new doctor to objectively assess changes in how the patient looked compared to before the first injection.

Patients also evaluated themselves for changes in the appearance of their wrinkles and folds. They looked at themselves in a mirror and compared how they looked now against their own picture taken before the first injection. They rated their results from “much improved” “much to worse”. (the scale included the following grades: 1-Much improved – 2-Improved – 3-No change – 4-Worse – 5-Much worse).

Patients reported their level of pain during and after injection using a scale from 0 to 100, with “0” meaning “no pain” and “100” meaning “the worst pain possible”. The pain was the most at the time of injection and was on average 23 out of 100. Five minutes after injection, the pain was on average 6 out of 100.

In the second study using a cannula compared to a needle, 50 patients were involved. The study lasted 12 weeks (3 months) and took place at 4 different locations across the United States. The wrinkles to be treated were considered to be moderate or severe, based on their depth. The patients were injected with RHA®4 on one side of their face with a **cannula** and with a needle on the other side. Study patients were mostly females, with light to very dark skin color. The majority of patients had light to medium skin tone.

Four weeks after the initial injection, the study patients were examined by their doctor. If their doctor felt it was necessary, he / she injected more RHA®4 (**touch-up**) to get the desired result.

Study patients kept a diary for 28 days after each injection to record **common treatment reactions** at the injection site. These diaries were then shared with their doctor.

Each patient saw their doctor at regular intervals for 12 to 16 weeks after the procedure. At each visit, the

doctor measured the effects of the treatments and checked the patient to evaluate any potential problem. Each patient was also examined by a doctor who did not know which side of their face was injected with the **cannula**. This allowed the new doctor to objectively assess changes in how the patient looked compared to before the first injection.

As for the first study, patients also evaluated themselves for changes in the appearance of their wrinkles and folds. They looked at themselves in a mirror and compared how they looked now against their own picture taken before the first injection. They rated their results from "much improved" to "much worse" (the scale included the following grades: 1-Much improved – 2- Improved – 3-No change – 4-Worse – 5-Much worse).

Patients reported their level of pain during and after injection using a scale from 0 to 100, with "0" meaning "no pain" and "100" meaning "the worst pain possible". The pain was the most at the time of injection and was on average 35 out of 100 with the cannula, and 41 out of 100 with the needle. Five minutes after injection, the pain was on average 3.5 out of 100 on either side of the face, there were no differences between the needle and the cannula side.

6. BENEFITS

What are the expected benefits of RHA®4?

RHA®4 smooths wrinkles and folds in moving (**dynamic**) areas of the face between the nose and the corners of the mouth (**nasolabial folds**). At 12 months, 77 patients were evaluated and at 15 months, 65 patients were evaluated. The evaluation was based on the depth of their wrinkles. In the clinical study, RHA®4 was shown to last 12 months in 87% of patients (67 out of 77 patients). At the end of the study, 15 months, RHA®4 was shown to last in 89% of patients (58 out of 65 patients).

At each office visit, a doctor who did not know which side of their face had RHA®4 injected, examined the patient. He/she evaluated the changes in appearance of the treated wrinkles compared to their appearance in the patient's picture taken before the treatment. These doctors reported that 84% of the patients (65 out of 77 patients) showed improvement at 12 months and 80% at 15 months (52 out of 65 patients).

At each office visit, study patients were asked whether their appearance had improved or gotten worse. The patient compared the appearance of his/her treated wrinkles against their own picture taken before the first injection. More than 87% of the patients reported that their wrinkles and folds were improved at both 12 and 15 months (end of the study) after the first injection.

Both cannula and needle injections help smooth the wrinkles and folds of the NLFs, with the same effectiveness. Moreover, treatment with both cannula and needle are safe and well tolerated.

7. RISKS

What were the common treatment reactions seen in the clinical study?

Most patients (95% or 114 out of 120 patients) experienced a **common treatment reaction** following their injection. Some patients experienced more than one. The expected reactions at the injection site are:

- Bruising
- Firmness
- Swelling
- Pain
- Tenderness

- Redness
- Lumps/bumps
- Change of skin color
- Itching

The duration of the **common treatment reactions** varied.

In the first study, the majority (68% or 445 of the 659 reactions) of the **common treatment reactions** were gone by 7 days after injection. Most (80% or 527 of the 659 reactions) of the **common treatment reactions** were gone by 14 days after injection. In the second study, most (73% or 376 of the 514 reactions) of the **common treatment reactions** were gone by 14 days after injection. Of those **common treatment reactions**, for both studies, the most frequent and majority reactions were swelling, firmness and tenderness at the site of injection.

For most of these reactions, patients reported that they were mild or moderate (91% or 597 of the 659 reactions) in the first study; 95%, or 208 of the 218 reactions that occurred with cannula and 95%, or 280 of the 296 that occurred with needle during the second study).) This means that the patient had little to no discomfort and their daily life was not affected. They may have used medication and/or make-up. Of the **common treatment reactions** that were reported as **severe** by the patients, lumps and bumps were the most frequent in both studies (9.4%, or 62 of the 659 reactions during the first study; 4.6%, or 10 of the 218 reactions that occurred with cannula and 5.4%, or 16 of the 296 that occurred with needle during the second study).

Table 1 and 2 give the percentage of study patients who experienced each **common treatment reaction** following the injection.

Table 1: **Common treatment reactions** observed in the first clinical study

Common Treatment Reactions	Study patients who reported the common treatment reaction
Swelling	81% (97 out of 120 patients)
Skin firmness	76% (91 out of 120 patients)
Tenderness	75% (90 out of 120 patients)
Redness	70% (84 out of 120 patients)
Lumps/Bumps	68% (81 out of 120 patients)
Bruising	58% (70 out of 120 patients)
Pain	55% (66 out of 120 patients)
Change in skin color	42% (50 out of 120 patients)
Itching	25% (30 out of 120 patients)

Table 2: **Common treatment reactions** observed after treatment using a needle or a **cannula** in the second clinical study

Common Treatment Reactions	Study patients who reported the common treatment reaction with cannula	Study patients who reported the common treatment reaction with needle
Skin firmness	80% (40 out of 50 patients)	86% (43 out of 50 patients)
Tenderness	76% (38 out of 50 patients)	88% (44 out of 50 patients)
Swelling	72% (36 out of 50 patients)	82% (41 out of 50 patients)
Lumps/Bumps	66% (33 out of 50 patients)	90% (45 out of 50 patients)

Redness	42% (21 out of 50 patients)	66% (33 out of 50 patients)
Pain	42% (21 out of 50 patients)	60% (30 out of 50 patients)
Bruising	20% (10 out of 50 patients)	54% (27 out of 50 patients)
Itching	20% (10 out of 50 patients)	34% (17 out of 50 patients)
Change in skin color	18% (9 out of 50 patients)	32% (16 out of 50 patients)

When **common treatment reactions** lasted longer than the 14 days of the diary (or 28 days in the second study), they were called **Treatment-Related Adverse Events (TRAEs)**. In the first study, the duration of TRAEs spanned from 1 to 90 days except for one event of appearance of reddish small blood vessels at the surface of the skin (moderate), which did not resolve before study exit but had resolved approximately 6 months later. In the second study, the duration of TRAEs spanned from 1 to 90 days except for eight events of feeling a small mass under the skin at injection site and injection swelling, which did not resolve before study exit (at 12 or 16 weeks) but had resolved approximately 1 month later (no longer than 20 weeks).

What other possible reactions could occur?

Other possible reactions can occur after the injection of a **dermal filler** such as RHA®4, although they were not observed in the clinical study. Possible reactions may be:

- Infection – Any time a **dermal filler** is injected under the skin there is a risk of infection at the site of injection. It may create hard and swollen lumps that may contain pus. Infection may require antibiotic treatment or other medical intervention.
- Granuloma – Red raised lumps that may appear weeks or months after injection. They may need to be treated by a doctor to make them go away. It may require additional procedures.
- Acne-like rashes – If you have a sensitive skin, the injection of a **dermal filler** may create an irritation or rash at the site of the treatment that can be compared to acne.
- Displacement of the gel – It is possible the injected gel may move out of the desired treatment area. Your appearance may be affected.
- Blisters – Any injection, including with RHA®4, may lead to formation of blisters at the point of injection.
- Scars – With any type of injection, including with RHA®4, scarring may occur.
- Scab – The injection of a **dermal filler**, such as RHA®4, may result in the skin becoming dry and crusty.
- Skin peeling (shedding) – The skin may dry as a reaction to the cleansing agent. The dry skin may be stressed with the injection and result in peeling or shedding.

Other less reported adverse reactions with RHA®4 product may occur such as edema, inflammatory reaction, erythema, abscess (a painful swollen area on or in the body that contains pus (= thick, yellow liquid)), overcorrection, pruritus (itching), skin necrosis, urticaria, angioedema (swelling in the deep layers of the skin), chapped lips (dry, cracked or sore lips), dermatitis (skin red and painful), fibrosis (excessive tissue growth), herpes breakout (recurrence of cold sore), influenza-like illness (flu like disease), localized numbness, pustules (a small raised area on the skin that contains pus), telangiectasia (transient dilation of blood vessels at injection site inducing a network-like aspect on the skin).

You should contact your doctor if you experience any of these reactions or if you notice anything unusual at the site of the treatment. Most of these reactions go away within a few days on their own but some may persist for more than 30 days. Your doctor may choose to treat them with medications.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Other serious reactions may occur following the injection of **dermal fillers** to smooth wrinkles. Contact your doctor immediately if any of these happen:

- One of the risks with using this product is unintentional injection into a blood vessel. The chances of this happening are very small, but if it does happen, the complications can be serious, and may be permanent. These complications, which have been reported for facial injections, can include vision abnormalities, blindness, stroke, temporary scabs, or permanent scarring of the skin. If you have changes in your vision, signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance of the skin, or unusual pain during or shortly after treatment, you should notify your health care practitioner immediately.
- Severe allergic reactions (anaphylaxis) - An **allergic reaction** to a material used to make a **dermal filler** that could occur shortly after the injection. Symptoms could include a rash, sneezing, itching, congestion or difficulty breathing.

You should discuss the potential treatment risks and benefits with your doctor before the injection.

8. PROCEDURE

What happens in the doctor's office before the treatment?

Note that each doctor may have their own process for treating patients.

Before the injection procedure, your doctor will ask you questions about your medical history. He/she will ask about your treatment goals. Your doctor will discuss whether you are a good candidate for RHA®4. He/she will review with you what to expect during and after treatment, including possible risks.

During this discussion, it is very important to tell your doctor about:

- all medications you are taking, both over the counter and prescription
- any previous facial treatment you may have received
- and any health conditions for which you are receiving medical attention

Your doctor will also examine your skin in and around the treatment area, and may take photos. The treatment area will be cleaned and prepared with a cleansing agent. Your doctor may use a pen to mark your face in the planned areas of injection.

Do the injections hurt?

Injections may cause some pain during and after the procedure. Your doctor will discuss different options for pain management with you. RHA®4 contains an **anesthetic** medicine (**lidocaine**) to help reduce injection site pain. This pain is temporary, and usually lessens within a few minutes. To prevent or reduce pain from the injection, your doctor may use ice packs, or other **anesthetic**, both before and after the injection.

What happens during the treatment?

RHA®4 is slowly injected into the facial skin in small amounts until your doctor sees the desired result which creates a more youthful appearance of the face. For most patients, the procedure only takes 15-30 minutes.

Once your doctor has finished injecting the treatment area, he/she may gently massage your face to help smooth and distribute the gel evenly.

Your doctor may also apply an ice pack to help decrease swelling and pain.

The amount of RHA®4 used depends on the depth of your wrinkles and your treatment goals. The right amount to be injected will be decided by your doctor during the procedure. Injection of additional RHA®4 (**touch-up** treatment) may be needed 2 to 4 weeks after initial treatment to achieve the desired aesthetic outcome. In the clinical study, 27% of the patients received a **touch-up** treatment 2 weeks after initial treatment to achieve their desired results. Your doctor will decide how much RHA®4 is needed for the **touch-up** treatment.

What happens after the treatment?

Your doctor may advise you to apply cold compresses to the treated area to help reduce pain and swelling. In order to prevent injury, ask your doctor how long you can leave ice packs on the treated area.

Be aware that numbness, short term loss of touch or feeling, and tingling around the injection area may occur due to the numbing medicine (**anesthetic**). It usually goes away within a few hours. Due to this numbness, you may not have normal feeling of hot or cold in this area.

Ask your doctor about any limits for exercising and exposure to sun, cold or heat (sauna, steam room). Exposure to any of these for the first 24 hours may increase short term redness, swelling, and/or itching at the injection site.

You should ask your doctor when make-up may be applied after your treatment. Using make-up too soon may increase the risk of infection or change in skin color.

Most **common treatment reactions** like bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change of skin color and itching go away on their own within a few days, but your doctor may choose to treat them with medications. In some rare worst cases situations, other procedure may be undertaken including incision and drainage (withdrawal of fluids from a wound, a sore) or excision (surgical removal) of the implant. Refer to section 7, RISKS.

When should I call my doctor?

Call your doctor if you have any questions or concerns after your procedure.

Call your doctor immediately if you have:

- Signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion)
- Changes in your vision
- Pain which increases after your treatment
- Significant pain away from the injection site
- Significant whitening or darkening of the skin
- Any treatment reaction other than bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, itching, which occurs in the first two weeks
- Any treatment reaction in the treated area, including lump or hardening under the skin, that appears weeks or months after your injection

The following are common reactions often seen after treatment with **dermal fillers**. They usually go away within 2 weeks. If you are concerned, or if they last more than 2 weeks, call your doctor:

- Bruising

- Firmness
- Swelling
- Pain
- Tenderness
- Redness
- Lumps/bumps
- Change in skin color
- Itching

9. ADDITIONAL INFORMATION

In case you have any further questions, please contact Revance Therapeutics, Inc. at 877-3REV-NOW (877-373-8669).

www.revance.com

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RHA®4 for Cheek fullness

Patient Information Brochure

Please read this document carefully before your treatment, it contains important information about RHA®4.

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1. GLOSSARY

Note: the terms in the glossary are **bold** throughout the document.

Allergic reaction: allergic reactions occur when a person's immune system (needed to fight infections) overreacts to substances that are harmless for most people. Symptoms could include a rash, sneezing, itching, congestion or difficulty breathing

Anaphylaxis: a severe **allergic reaction** which needs medical treatment right away

Anesthetic: a medication that reduces pain; it can be added to a cream or a **dermal filler**; sometimes called a numbing medicine

Anticoagulants: medications that thin your blood

Anti-inflammatory: a medicine which reduces pain, heat, redness, and swelling, which are symptoms of inflammation

BDDE: 1,4-butanediol diglycidyl ether, a chemical compound used in very small amount to bind the chains of **HA** together to form a gel

Cannula: a thin metal tube with a blunt tip. It may be used as an alternative to needles for injections

Cheeks: area of injection as illustrated in Figure 1

Common treatment reaction: reactions which can be expected after injection of a **dermal filler**. It includes bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change in skin color, and itching

Dermal filler: material which is injected under the skin to help smooth and plump the cheeks

Dynamic: able to move, not fixed in place, such as the skin on the face

Granuloma: localized hardening under the skin, like a lump, appearing weeks or months after the injection

Herpes: a virus which causes certain skin conditions, such as cold sores

Hyaluronic Acid (HA): a naturally occurring substance found in the human body which helps maintain skin structure and feel. The HA found in RHA®4 is a different form than the HA found in the human body

Immunosuppressive therapy: medications that reduce the body's normal response to infections, allergens, anything not normally found in the body

Keloid: a thick tough scar

Lidocaine: a type of **anesthetic** medication which helps reduce pain

Pigmentation disorders: general term to refer to health conditions that affect the color of the skin

Severe common treatment reaction: reaction following an injection with symptoms that caused severe discomfort, compromised the performance of daily activities and for which treatment of the symptoms was needed. The severity is determined by the patient.

Streptococcus equi: a bacteria, which does not cause illness in people, used to make the **hyaluronic acid**

Therapy: treatment intended to reduce, heal or cure pain, disease or physical reaction

Touch-up: an additional injection, performed 2 to 4 weeks after the initial injection. Some patients may require a touch-up treatment to achieve the desired aesthetic results

Treatment Related Adverse Events (TRAEs): any unusual medical occurrence in a subject following the injection which is related to the dermal filler as determined by the doctor. It may be any symptoms, disease or reaction associated with the use of the dermal filler.

2. PRODUCT DESCRIPTION

What is RHA®4?

RHA®4 is an injectable gel (also called a **dermal filler**) used to augment volume of the **cheeks** to correct age-related volume deficiencies. It is injected into the **cheek**, a moving (**dynamic**) area (see Figure 1). It is approved for use in adults over 22 years of age.

RHA®4 is produced with **hyaluronic acid (HA)**, using an advanced technology to obtain a soft and long-lasting injectable gel to increase **cheek** volume. Chains of **HA** are linked together through a chemical reaction triggered by a small quantity of **BDDE** to create the gel texture of RHA®4. The **HA** of the gel is made from a non-animal source.

RHA®4 contains a small amount of an **anesthetic** medicine (**lidocaine**), to help reduce discomfort during injection. The effect of the anesthetic is temporary, some discomfort may be experienced due to the injection of the filler during and after the procedure.

Hyaluronic acid (HA) is a naturally occurring substance found in the human body. Your body's own **HA** helps maintain the skin's structure and its natural feel.

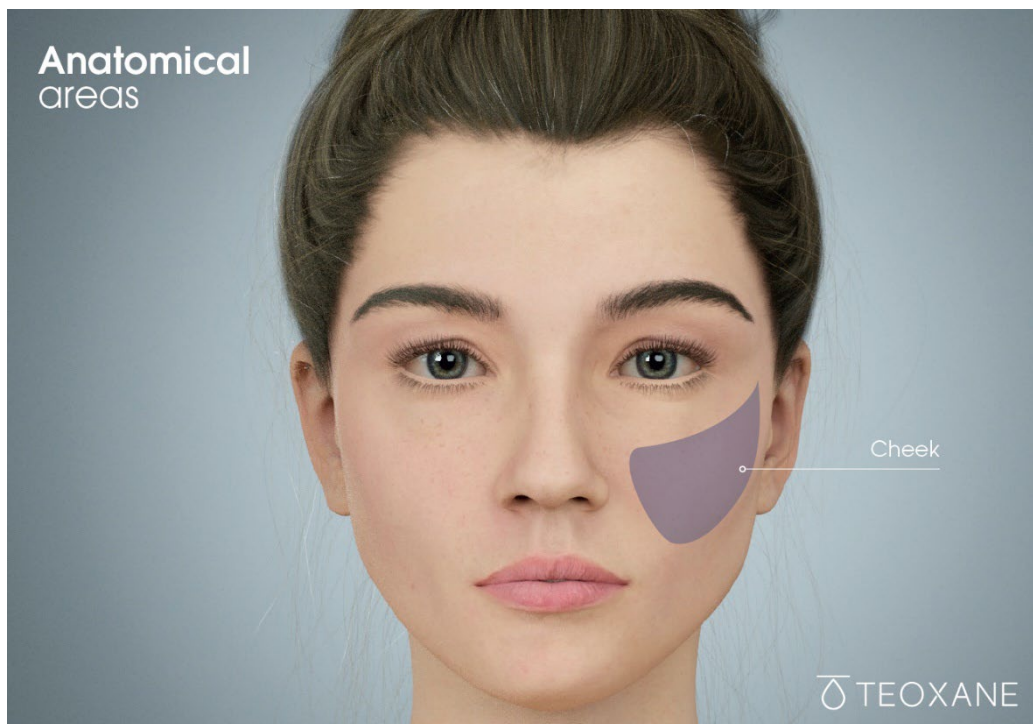


Figure 1: Location of **cheek** area

How does it work?

RHA®4 is injected into the skin with an ultrafine needle or a small, blunt-tipped **cannula** to add volume to the **cheek** area and creates a more defined contour and a younger-looking face. This volumizing effect has been shown to last 6 months in 79% of the patients (103 out of 130 patients) and lasted 12 months in 66% of the patients (84 out of 128 patients).

RHA®4 is not a permanent gel. It slowly goes away as the body absorbs the gel. The volumizing effect will gradually disappear.

3. CONTRAINDICATIONS

Are there any reasons why I should not receive RHA®4?

Your doctor will ask about your medical history to see if RHA®4 is right for you. You should not use RHA®4 if you have a history of:

- severe **allergic reactions (anaphylaxis)** or history or presence of multiple severe allergies. An injection of RHA®4 may result in an **allergic reaction**.
- **allergic reactions** to the material (from ***Streptococcus equi***) used to make the **HA** in RHA®4. An injection of RHA®4 may result in an **allergic reaction**.
- **allergic reactions** to **lidocaine** or other similar substances used to reduce pain. An injection of RHA®4 may result in an **allergic reaction**.
- **bleeding disorders**. Any injection, including RHA®4 and other **dermal fillers**, may result in a higher risk of bruising or bleeding in the treated area.

4. **PRECAUTIONS**

Are there precautions that I should discuss with my doctor?

The following are important treatment considerations that you should discuss with your doctor. These hazards, if not avoided, could result in unsatisfactory results or complications:

- Tell your doctor if you are under 22 years of age. RHA®4 has not been studied in people younger than 22 and the effects are not known.
- Tell your doctor if you are pregnant (or plan to be) or breastfeeding. RHA®4 has not been studied in women who were pregnant or breastfeeding and the effects are not known.
- Tell your doctor if you are taking medicine that reduces your body's ability to fight infection (**immunosuppressive therapy**). Taking this type of medicine may increase the risk of infection following the injection of RHA®4 or other **dermal fillers**.
- Be sure to tell your injecting doctor if you are using "blood thinners" (**anticoagulants**), or any other medications that affect bleeding. Do not stop taking them until you speak with the doctor who prescribed them for you. Tell your prescribing doctor that you are considering having your **cheeks** treated with RHA®4. These blood thinning medications may cause increased bleeding and/or bruising in the treated area.
- Tell your doctor if you have a history of cold sores (**herpes**). Any injection, including RHA®4, in the general area may trigger a recurrence of your cold sores (**herpes**).
- Tell your doctor if you have an injury, or other skin condition near the injection site(s). Injection of a **dermal filler** in this situation may lead to a worsening of your condition or infection. You may have to wait until you are completely healed before using RHA®4.
- Tell your doctor if you have ever developed a thick tough scar (**keloid**) or had problems with skin discoloration. It is possible that injection of any **dermal filler**, including RHA®4, may make the skin thicker and change color. However, when RHA®4 was studied in patients with different skin tones (pale to dark), there were no reports of this happening.
- Tell your doctor if you have a history of **pigmentation disorders**. The safety of RHA®4 in patients with history of **pigmentation disorders** has not been studied. Use in these patients may result in changes in pigmentation.
- Tell your doctor if you have already been injected with **dermal fillers** in the same area as the one(s) you are about to be treated for. This information helps your doctor decide when and whether you should get treatment with RHA®4.
- Tell your doctor if you have recently had (within 6 months), or are considering, laser treatment, chemical peeling or any other facial procedure. Use of RHA®4 with these skin treatments may lead to an increased severity of the **common treatment reactions** such as redness, swelling, heat or pain in the area.
- You should not take Vitamin E, aspirin, or **anti-inflammatories** during the week prior to the injection. Taking these medications can thin your blood and may result in increased bleeding and/or more bruising in the treated area.

If you have any additional questions about any topic in this section, please discuss further with your doctor.

5. HOW WAS RHA®4 STUDIED?

RHA® 4 was tested in a clinical study to make sure it worked as intended and was safe to use. The study was conducted to test the effectiveness and safety of RHA® 4 in improving **cheek** fullness. This study lasted 52 weeks (12 months) and involved 201 patients. The patients who  were treated presented with moderate or severe volume loss of their **cheeks**, based on their fullness. They were injected with either RHA® 4 or with an other dermal filler used as a control. Study patients were mostly females, with light to very dark skin color. The study took place at 8 different locations across the United States.

Four weeks after the initial injection, the study patients were examined by their doctor. If their doctor felt it was necessary, **touch-up** injections were given as needed with the same product as used at the initial treatment to get the desired result.

Study patients kept a diary for 30 days after each injection to record **common treatment reactions** at the injection site. These diaries were then shared with their doctor.

Each patient saw their doctor at regular intervals for 52 weeks after the procedure. All subjects were followed for an additional 12 weeks if they had received repeated treatment at the end of the study. At each visit, the doctor measured the effects of the treatments and checked the patient to make sure there were no problems. Each patient was also examined by a doctor who did not know which product was injected. This allowed the new doctor to objectively assess changes in how the patient looked compared to before the first injection, without knowing which product was injected.

Patients also evaluated themselves for changes in the appearance of their **cheeks**. They looked at themselves in a mirror and compared how they looked now against their own picture taken before the first injection. They rated their results from “much improved” to “much worse” (the scale included the following grades: 1-Much improved – 2-Improved – 3-No change – 4-Worse – 5-Much worse). Patients also assessed how satisfied they were with their **cheeks** at rest and when smiling (symmetry, smoothness, attractiveness, contour and youthful fullness). Patients reported their level of pain during and after injection using a scale from 0 to 100, with “0” meaning “no pain” and “100” meaning “the worst pain possible”. The pain was the most at the time of injection and was on average 7 out of 100. Five minutes after injection, the pain was on average 3 out of 100.

6. BENEFITS

What are the expected benefits of RHA®4?

RHA® 4 will temporally add volume to your **cheeks**. At 8 weeks, 137 patients were evaluated and at 52 weeks (1 year), 128 patients were evaluated. The evaluation was based on the fullness of their **cheeks**. In the clinical study, RHA® 4 had a visible effect in 88% of patients (120 out of 137 patients) at 8 weeks. At the end of the study, 52 weeks (1 year), RHA® 4 still had a visible effect in 66% of patients (84 out of 128 patients).

At each office visit, a doctor who did not know which product was injected (RHA® 4 or the other product), examined the patient. They evaluated the changes in volume of the treated **cheeks** compared to their appearance in the patient's picture taken before the treatment. These doctors reported that 94% of the patients (129 out of 137 patients) showed improvement at 8 weeks, 76% (97 out of 128 patients) at 52 weeks. At each office visit, study patients were asked whether their appearance had improved or worsened. The patient compared the fullness of their treated **cheeks** against their own picture taken before the first injection. 96% of the patients reported that their **cheeks** were improved at 8 weeks. More than 81% of the patients reported that their **cheeks** were improved at 52 weeks (end of study) after the last injection (initial injection or touch-up).

At each study visit, patients completed satisfaction questionnaires, about the satisfaction with their **cheeks**, at rest and when smiling. Patients reported very high satisfaction score with their **cheeks** at both rest and when smiling through 1 year.

Finally, over 95% of patients thought their **cheeks** looked natural 1 year after treatment.

7. **RISKS**

What were the common treatment reactions seen in the clinical study?

Most patients (91%, 128 out of 141 patients) experienced a **common treatment reaction** following their injection. Some patients experienced more than one. The expected reactions at the injection site are:

- Bruising
- Firmness
- Swelling
- Pain
- Tenderness
- Redness
- Lumps/bumps
- Change of skin color
- Itching

The duration of the **common treatment reactions** varied. The majority (68%, 87 of the 128 patients) of patients had their **common treatment reactions** resolved 14 days after injection. Of those **common treatment reactions** which lasted for 30 days or more (occurring in 13% of the patients, 18 of the 128 patients, the most frequent were lumps/bump and firmness at site of injection.

For most of these reactions, patients reported that they were mild or moderate (95%, 121 of the 128 reactions). This means that the patient had little to no discomfort and their daily life was not affected. They may have used medication and/or make-up. Of the **common treatment reactions** that were reported as severe by the patients (5%, 7 of the 128 reactions), the most frequent were firmness. After 30 days, all the **common treatment reactions** were mild.

Table 1 gives the percentage of study patients who experienced each common treatment reaction following the injection.

*Table 1: **Common treatment reactions** observed in the clinical study*

Common Treatment Reactions	Study patients who reported the common treatment reaction
Tenderness	80% (113 out of 141 patients)
Skin firmness	77% (108 out of 141 patients)
Swelling	69% (98 out of 141 patients)
Lumps/Bumps	55% (77 out of 141 patients)
Bruising	52% (74 out of 141 patients)
Pain	50% (70 out of 141 patients)
Redness	43% (61 out of 141 patients)

Change in skin color	23% (32 out of 141 patients)
Itching	12% (17 out of 141 patients)

When **common treatment reactions** lasted longer than the 30 days of the diary or if treatment reactions were not considered typical in type and/or duration and/or severity, they were called **Treatment-Related Adverse Events (TRAEs)**. All **Treatment-Related Adverse Events** were mild or moderate. No severe Treatment-Related Adverse Events were observed. The vast majority of **Treatment-Related Adverse Events** (82%) resolved within 14 days, four events lasted between 30 and 90 days and 1 event lasted 227 days.

All **Treatment-Related Adverse Events** eventually resolved without consequence.

What other possible reactions could occur?

Other possible reactions can occur after the injection of a **dermal filler** such as RHA®4, although they were not observed in the clinical study. Possible reactions may be:

- Infection – Any time a **dermal filler** is injected under the skin there is a risk of infection at the site of injection. It may create hard and swollen lumps that may contain pus. Infection may require antibiotic treatment or other medical intervention.
- Granuloma – Red raised lumps that may appear weeks or months after injection. They may need to be treated by a doctor to make them go away. It may require additional procedures.
- Acne-like rashes – If you have a sensitive skin, the injection of a **dermal filler** may create an irritation or rash at the site of the treatment that can be compared to acne.
- Displacement of the gel – It is possible the injected gel may move out of the desired treatment area. Your appearance may be affected.
- Blisters – Any injection, including with RHA®4, may lead to formation of blisters at the point of injection.
- Scars – With any type of injection, including with RHA®4, scarring may occur.
- Scab – The injection of a **dermal filler**, such as RHA®4, may result in the skin becoming dry and crusty.

Other less reported adverse reactions with RHA®4 product may occur such as edema, skin peeling (dry skin and shedding), inflammatory reaction, abscess (a painful swollen area on or in the body that contains pus (= thick, yellow liquid)), overcorrection, skin necrosis, urticaria, angioedema (swelling in the deep layers of the skin), chapped lips (dry, cracked or sore lips), dermatitis (skin red and painful), fibrosis (excessive tissue growth), herpes breakout (recurrence of cold sore), localized numbness, pustules (a small raised area on the skin that contains pus), telangiectasia (transient dilation of blood vessels at injection site inducing a network-like aspect on the skin).

You should contact your doctor if you experience any of these reactions or if you notice anything unusual at the site of the treatment. Most of these reactions go away within a few days on their own but some may persist for more than 30 days. Your doctor may choose to treat them with medications.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Other serious reactions may occur following the injection of **dermal fillers** to smooth wrinkles. Contact your doctor immediately if any of these happen:

- One of the risks with using this product is unintentional injection into a blood vessel. The chances of this happening are very small, but if it does happen, the complications can be serious, and may be permanent. These complications, which have been reported for facial injections, can include vision abnormalities, blindness, stroke, temporary scabs, or permanent scarring of the skin. If you have changes in your vision, signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance of the skin, or unusual pain during or shortly after treatment, you should notify your health care practitioner immediately.
- Non-severe and severe allergic reactions (anaphylaxis) - An **allergic reaction** to a material used to make a **dermal filler** that could occur shortly after the injection. Symptoms could include a rash, sneezing, itching, congestion or difficulty breathing.

You should discuss the potential treatment risks and benefits with your doctor before the injection.

8. PROCEDURE

What happens in the doctor's office before the treatment?

Note that each doctor may have their own process for treating patients.

Before the injection procedure, your doctor will ask you questions about your medical history. He/she will ask about your treatment goals. Your doctor will discuss whether you are a good candidate for RHA®4. He/she will review with you what to expect during and after treatment, including possible risks.

During this discussion, it is very important to tell your doctor about:

- all medications you are taking, both over the counter and prescription
- any previous facial treatment you may have received
- and any health conditions for which you are receiving medical attention

Your doctor will also examine your skin in and around the treatment area and may take photos. The treatment area will be cleaned and prepared with a cleansing agent. Your doctor may use a pen to mark your face in the planned areas of injection.

Do the injections hurt?

Injections may cause some pain during and after the procedure. Your doctor will discuss different options for pain management with you. RHA®4 contains an **anesthetic** medicine (**lidocaine**) to help reduce injection site pain. This pain is temporary, and usually lessens within a few minutes. To prevent or reduce pain from the injection, your doctor may use ice packs, or other **anesthetic**, both before and after the injection

What happens during the treatment?

RHA®4 is slowly injected into the **cheeks** in small amounts until your doctor sees the desired result which is to increase your **cheek** volume. For most patients, the procedure only takes 15-30 minutes.

Once your doctor has finished injecting the treatment area, he/she may gently massage your face to help smooth and distribute the gel evenly.

Your doctor may also apply an ice pack to help decrease swelling and pain.

The amount of RHA®4 used depends on the volume loss of your **cheeks** and your treatment goals. The right amount to be injected will be decided by your doctor during the procedure. Injection of additional RHA®4 (**touch-up** treatment) may be needed 2 to 4 weeks after initial treatment to achieve the desired aesthetic outcome. In the clinical study, 63% of the patients received a **touch-up** treatment 4 weeks after initial treatment to achieve their desired results. Your doctor will decide how much RHA®4 is needed for the **touch-up** treatment.

What happens after the treatment?

Your doctor may advise you to apply cold compresses to the treated area to help reduce pain and swelling. In order to prevent injury, ask your doctor how long you can leave ice packs on the treated area.

Be aware that numbness, short term loss of touch or feeling, and tingling around the injection area may occur due to the numbing medicine (**anesthetic**). It usually goes away within a few hours. Due to this numbness, you may not have normal feeling of hot or cold in this area.

Ask your doctor about any limits for exercising and exposure to sun, cold or heat (sauna, steam room). Exposure to any of these for the first 24 hours may increase short term redness, swelling, and/or itching at the injection site.

You should ask your doctor when make-up may be applied after your treatment. Using make-up too soon may increase the risk of infection or change in skin color.

Most **common treatment reactions** like bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, change of skin color and itching go away on their own within a few days, but your doctor may choose to treat them with medications. In some rare worst cases situations, other procedures may be undertaken including incision and drainage (withdrawal of fluids from a wound, a sore) or excision (surgical removal) of the implant. Refer to section 7 RISKS.

When should I call my doctor?

Call your doctor if you have any questions or concerns after your procedure.

Call your doctor immediately if you have:

- Signs of a stroke (including sudden difficulty speaking, numbness or weakness in your face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion)
- Changes in your vision
- Pain which increases after your treatment
- Significant pain away from the injection site
- Significant whitening or darkening of the skin
- Any treatment reaction other than bruising, firmness, swelling, pain, tenderness, redness, lumps/bumps, itching, which occurs in the first two weeks
- Any treatment reaction in the treated area, including lump or hardening under the skin, that appears weeks or months after your injection

The following are common reactions often seen after treatment with **dermal fillers**. They usually go away within 2 weeks. If you are concerned, or if they last more than 2 weeks, call your doctor:

- Bruising
- Firmness
- Swelling
- Pain

- Tenderness
- Redness
- Lumps/bumps
- Change in skin color
- Itching

9. ADDITIONAL INFORMATION

In case you have any further questions, please contact Revance Therapeutics, Inc. at 877-3REV-NOW (877-373-8669).

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