About Restylane® Refyne

Before beginning your treatments, please review this important information.

1. GLOSSARY

Anesthetic – a medication (or "treatment") that reduces pain

Dermal filler – a material that is injected underneath the skin to smooth a wrinkle or restore volume to an area of skin

Hyaluronic acid – a naturally occurring sugar found in the body that gives the skin moisture, volume, and elasticity.

Hyaluronidase – an enzyme that breaks down hyaluronic acid

Lidocaine – a commonly used local anesthetic to numb the skin, see "anesthetic"

Nasolabial folds – the medical term for the creases that run from the sides of your nose to the corners of your mouth. Commonly known as "laugh lines"

XpresHAn Technology™ –the unique manufacturing process used to make Restylane Refyne hyaluronic acid injectable gel

Pigmentation disorder – A disorder that results in a change in skin color

Topical –a cream or ointment applied to the top of the skin, affecting only the area to which it is applied

Touch-up – an additional injection of dermal filler that is usually given a short time after the initial injection. Some patients may require a touch-up treatment to achieve the desired result

2. PRODUCT DESCRIPTION

What is Restylane Refyne?

Restylane Refyne is a dermal filler injected under the (facial) skin. Once in place, it helps smooth away your "laugh lines" – the wrinkles and folds that may form at the sides of your nose and run down toward the corners of your mouth.

Restylane Refyne is made out of hyaluronic acid - a naturally occurring sugar, found in the body that gives the skin moisture, volume, and elasticity – and a small amount of lidocaine, which is a commonly used local anesthetic to numb the skin.

Restylane Refyne is made using a manufacturing process called XpresHAn Technology™, which creates a smooth, injectable gel that can give your skin a natural, soft look

3. INDICATIONS FOR USE

What is Restylane Refyne for?

As you age, your facial skin begins to lose its elasticity and volume. As a result, your "laugh lines", the creases that run from the sides of your nose toward the corners of your mouth, become more pronounced. Restylane Refyne injectable gel is designed to temporarily help counter this by smoothing out these wrinkles and folds and restoring a natural, soft look to your face. Restylane Refyne has been shown to maintain this effect for up to 12 months.

Note: Facial features can differ. Speak to your doctor about the lines on your face that are appropriate for treatment with Restylane Refyne.

How is Restylane Refyne used?

Restylane Refyne is injected into the facial skin through a small needle to smooth facial wrinkles and folds (laugh lines), resulting in a more youthful appearance of the skin. For most patients, the procedure only takes 15 – 30 minutes.

4. CONTRAINDICATIONS

Are there any reasons why I should not receive Restylane Refyne?

Before using Restylane Refyne, your doctor will talk to you about your medical history to determine if you are an appropriate candidate for treatment. You will be asked questions about possible allergies to ensure that Restylane Refyne can be safely administered. Tell your doctor about all of your medical conditions, including if you:

- Have severe allergies with a history of severe reactions (anaphylaxis). Use of Restylane Refyne may result in an allergic reaction.
- Are allergic to the anesthetic lidocaine or to any of the proteins used to make the hyaluronic acid in Restylane Refyne (bacterial proteins). Use may result in an allergic reaction.

If you are not sure about your medical history concerning these allergies, please discuss further with your doctor.

5. PRECAUTIONS

What precautions should my doctor advise me about?

The following are important treatment considerations for you to discuss with your doctor and understand in order to help avoid unsatisfactory results and complications.

- Restylane Refyne helps treat laugh lines – the natural facial wrinkles and folds that can occur due to aging. Restylane Refyne has not been tested to treat any other types of wrinkles.

- 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 doctor immediately.
- You have had any prior surgery or procedures in the area you intend to be treated with Restylane Refyne.
- The use of Restylane Refyne if you have skin sores, pimples, rashes, hives, cysts, or infections should be postponed until healing is complete. Use of Restylane Refyne in these instances could delay healing or make your skin problems worse.
- Restylane Refyne is for adults ages 22 and older.
- The safety of Restylane Refyne has not been studied in women who are pregnant or breastfeeding. The risk of using Restylane Refyne in pregnant or breastfeeding women is unknown. Talk to your doctor before using Restylane Refyne if you are pregnant, planning to become pregnant, or breastfeeding.
- You may have a greater risk of developing an infection if you use Restylane Refyne while taking any medication that reduces your body's natural defense system. These medications are called "immunosuppressants" because they stop your body's immune system from functioning normally. Tell your doctor about any medication you are taking.
- Some medication like aspirin and warfarin can thin your blood, which may increase your risk of bleeding or prolong any bleeding that occurs. These medications also increase your risk of bruising or bleeding at the injection site. Tell your doctor about any medication you are taking.
- As with any injection procedure, you may have a higher risk of bruising or bleeding at the injection site if you have a bleeding disorder.
- If you have any history of scarring, particularly thick and stiff scars, or any skin color (pigmentation) disorders, talk to your doctor about this before your procedure. Scarring and skin color changes can occur with hyaluronic acid fillers in general. When Restylane Refyne was studied in patients with different skin tones (pale to dark), there were no reports by patients of excessive scarring (keloids) or changes in skin color.
- The use of Restylane Refyne with skin therapies such as laser treatment or chemical peels may lead to other side effects such as redness, swelling, heat and/or pain of the skin (inflammatory reaction). Tell your doctor if you have had any of these procedures.
- Within the first 24 hours after treatment with Restylane Refyne, you should avoid or minimize hard (strenuous) exercise. You should also minimize exposure to extensive sun or heat, as any of these may cause temporary redness, swelling, and/or itching at the injection site. An ice pack (in a suitable cloth, avoiding any direct contact with the skin) can be applied for relief if needed.
- You have a dental block or use topical lidocaine at the same time as the filler treatment. High doses of lidocaine could cause a toxic reaction.
- If you have any additional questions about any topic in this section, please discuss further with your doctor.

6. Clinical Studies

How was Restylane Refyne Studied?

Restylane Refyne was tested to ensure that it worked properly (effective) and was safe to use, in 170 patients before it was approved for use in all patients. These patients included 160 women, 10 men, and were from various ethnic groups with multiple skin tones (pale to dark skin). Each of these patients expressed desire to improve the appearance of their facial wrinkles and folds (laugh lines).

The study was created to compare two different dermal filler gel products. It was conducted by 12 different doctors in 12 different locations across the United States.

Patients who participated in the study received an initial treatment with Restylane Refyne on one side of their face and another, similar dermal filler gel, without anesthetic, on the other side of their face. Touch-up injections were given as needed, and each patient was monitored for 12 months following the procedure to measure the effects of the treatments. For each patient, the amount of product used was based on their individual needs.

In order to objectively measure improvements in appearance over 12 months, each patient was evaluated by a doctor other than one who had performed the treatment. Patients also evaluated themselves. To measure side effects following the procedure, each patient kept a diary for 21 days to record side effects. These were then shared with the doctors.

7. BENEFITS

What will Restylane Refyne do for me?

- Restylane Refyne temporarily reduces signs of aging on your face by smoothing the wrinkles and folds that form around your nose and extend down to the corners of your mouth (laugh lines). This natural, smooth look should last for up to 12 months.
- Restylane Refyne was studied in many patients like yourself to determine if it was effective in treating laugh lines and to ensure that it is safe for use.

The study doctors reported:

- 79% of patients had at least a 1-point improvement in wrinkle appearance 6 months after treatment
- 62% of patients had at least a 1-point improvement in wrinkle appearance 1 year after treatment

The patients reported:

- 79% rated an improvement in the appearance of their wrinkles 6 months after treatment
- 67% rated an improvement in the appearance of their wrinkles 1 year after treatment

For further information regarding the results of the clinical study, see Section 6.

8. RISKS

What side effects were seen in the clinical study?

In the study of Restylane Refyne, most patients reported the following side effects at the site where they received the injection:

- Swelling
- Bruising
- Lumps/Bump Formation
- Pain/Tenderness
- Itching
- Redness

Most patients said their side effects were mild, short-lived and did not require them to call their doctor. These patients said that their side effects disappeared within 1-2 weeks.

Patients also reported that the anesthetic lidocaine, which is part of the Restylane Refyne injection and used to numb the injection site, significantly reduced pain during and after their procedure.

The table below provides additional information about the side effects that patients reported in this study.

Table 1 - Most common side effects of Restylane Refyne recorded by patients who participated in the study, reported in their 21-day diary.

Side Effect	Number of patients
Swelling	101 out of 170 people (59%)
Bruising	96 out of 170 people (56%)
Lump/Bump Formation	75 out of 170 people (44%)
Pain/Tenderness	72 out of 170 people (42%)
Itching	25 out of 170 people (15%)
Redness	9 out of 170 people (5%)

It is important to understand that any procedure carries a risk of side effects. After an injection of dermal filler gel, you may experience skin reactions due to the injection and/or from the dermal filler gel.

When Restylane Refyne was studied, side effects that occurred at the injection site included swelling, bruising, small bumps, pain/tenderness, itching and redness. These were mild to moderate reactions that disappeared within 1-2 weeks. If any symptoms last longer than 2 weeks, you should call your doctor.

Other potential risks may arise from an injection of a dermal filler gel such as Restylane Refyne including the following:

- Infection - Any time a dermal filler gel like Restylane Refyne is injected into facial skin there is risk of infection, which could appear as small, swollen or red bumps. These are called inflammatory papules. These infections are rare, however you should talk to your doctor about further treatment if you see any of these signs or symptoms.
- Scarring - While it is very rare, scarring may occur with an injection procedure. When Restylane Refyne was studied, there was no excessive scarring (a condition called keloids) observed in patients who received Restylane Refyne.
- Change in skin tone - If you are African American, you may have a higher risk of darkening of the skin tone (hyperpigmentation) in the treated area. This may take several weeks to disappear. When Restylane Refyne was studied, this change in skin tone did not occur in patients who received Restylane Refyne.
- Cold sores - If you have had cold sores in the past, there is a risk that they will return after your procedure with Restylane Refyne.
- Age and pregnancy – Restylane Refyne has not been studied in patients under 18 years of age, patients who are pregnant or patients who are breastfeeding. If you are pregnant, trying to become pregnant, or breastfeeding, the safety and effectiveness of Restylane Refyne has not been proven in patients like yourself.
- Vision changes - Vision abnormalities have rarely been reported after treatment with other dermal filler gel treatments.
- Use of other skin therapies - The safety of Restylane Refyne has not been established in patients who have had other skin therapies, such as laser, mechanical, or chemical peeling, and hair removal. If you use Restylane Refyne with any of these skin therapies you may experience other side effects such as redness, swelling, heat and/or pain of the skin (inflammation).
- Ultraviolet (UV) exposure - You should avoid exposing the area(s) treated with Restylane Refyne to excessive sun, UV lamps or indoor tanning beds/booths, and extreme heat and cold until any redness or swelling has disappeared. Exposure to UV sources may result in irritation at the site of treatment.
- One of the risks of Restylane Refyne is that it may be unintentionally injected into a blood vessel during the procedure. 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, or blindness,
    - stroke,
    - temporary scabs,
    - permanent scarring of the skin.

You should tell your doctor immediately if you experience any of these side effects or if you notice anything unusual at the site of treatment. There are also other potential side effects that can occur with dermal filler gel injections. Although most side effects will resolve with time, some side effects may

persist longer than 30 days. Your doctor may choose to treat them with medications, such as antibiotics, steroids, or hyaluronidase (an enzyme that breaks down HA). You should discuss the potential treatment risks and benefits with your doctor.

What side effects have been voluntarily reported following use of Restylane Refyne with and without lidocaine in and outside of the United States?

The most common reported side effects included reports of temporary swelling (edema) with immediate onset or delayed onset, up to several weeks after treatment. The following events were also reported in decreasing order of frequency:

- lumps or bumps (mass) /hardening (induration)
- skin redness (erythema)
- pain/tenderness
- small bumps (papules/nodules)
- bruising (hematoma)
- short duration of effect
- skin discoloration/darkening skin tone (hyperpigmentation)
- restricted blood flow (ischemia/necrosis) including white skin (pallor)
- presumptive bacterial infection/pockets of pus (abscess formation)
- injection site reactions including burning sensation, discomfort, dryness, exfoliation, irritation and warmth
- allergic reaction (hypersensitivity) /rapid swelling (angioedema)
- inflammation
- implanted gel moving from site of injection (device displacement)
- itching (pruritus)
- uneven appearance of the skin (deformity/overcorrection)
- reduced sense of touch (hypoesthesia), tingling sensation (paraesthesia)
- eye disorders such as eye swelling, blurred vision, ocular discomfort, and visual disturbance
- small area of inflammation in tissue (granuloma/foreign body reaction)
- blisters/vesicles
- rash
- scarring
- acne
- hives (urticaria)
- leakage from implant site (discharge)
- symptoms of reactivation of herpes infection
- skin inflammation (dermatitis)
- muscle disorders such as muscle twitching and muscle spasm
- dilated small blood vessels (telangiectasia)
- non dermatological events including chills, dizziness and shortness of breath (dyspnoea) and headache
- other dermatological events including dry skin, chapped lips and blistering skin (epidermolysis)

When required, treatments for these events included ice, massage, warm compress, local drugs that widen blood vessels, drugs to reduce inflammation (corticosteroids), antibiotics, drugs to relieve

allergy symptoms (antihistamines), drugs to relieve pain (analgesics), medicine to relieve the body of excess fluid (diuretic agents), surgical procedure (incision, drainage or excision), surgery or an enzyme used to help break down hyaluronic acid (hyaluronidase).

Reports of serious adverse events for Restylane Refyne with and without lidocaine are rare. The most commonly reported serious adverse events were injury due to restricted blood flow (ischemia/necrosis), eye disorders, infection/pocket of pus (abscess) and allergic reaction (hypersensitivity). Other concurrent serious adverse events included swelling, bruising/bleeding, skin discoloration, skin redness (erythema) and pain/tenderness.

Serious infection/pocket of pus (abscess) were mostly reported with a time to onset ranging from one day up to 4 months following the injection. Most of the patients were recovering at the time of last contact. The treatments may include antibiotics, drugs to relieve pain (analgesics), drugs to reduce inflammation (corticosteroids) and an enzyme used to help break down hyaluronic acid (hyaluronidase).

The onset of serious allergic reactions (hypersensitivity) generally vary from immediately to a few weeks post injection. Most of the events were recovering or recovered at the time of last contact. The treatments may include drugs to relieve pain (analgesics), drugs to relieve allergy symptoms (antihistamine), antibiotics, and drugs to reduce inflammation (corticosteroids).

Blockage of a blood vessel (vascular occlusion) resulting in restricted blood flow (ischemia/necrosis) and vision changes, have been reported following facial aesthetic treatments with injectable soft tissue fillers with a time to onset ranging from immediate to a few weeks following injection. Blockage of a blood vessel may occur due to an accidental injection into the blood vessel or as a result of local compression of the vessel (embolization), this may rarely affect other organs and rare cases of restriction in blood supply to tissues (ischemic events) after affecting the eye and brain have led to vision loss and stroke (cerebral infarction), respectively. Treatments may include medicine to prevent blood clotting (anticoagulant), medicine to treat allergic reactions (epinephrine), aspirin, an enzyme used to help breakdown hyaluronic acid (hyaluronidase), drugs to reduce inflammation (corticosteroids), drugs to relieve pain (analgesics), local drugs that widen blood vessels (vasodilating agents) including nitropaste, antibiotics, surgery (including drainage), and hyperbaric oxygen.

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.

9. Before Procedure Information

What happens in the office before the injection?

Note that each doctor may have a unique process for treating patients.

The following is an example of what your doctor may do before the injection procedure.

- Talk to you about your medical history including questions about prior procedures, surgeries, illnesses and medications you have taken.
- Talk to you about your desired results for your procedure.
- Examine your face and discuss whether Restylane Refyne is the right treatment for you.
- Review what you should expect during and after the procedure.
- Let you know of any possible side effects that you may experience, and what to do if you experience these.
- Take photos of the area of your face that will be treated.

Your doctor may also have additional ways of evaluating patients and preparing them for a procedure

10. PROCEDURE DESCRIPTION

What happens during the procedure?

Your doctor may do the following during your procedure:

- Your skin will be cleansed prior to treatment.
- Use a cream or ointment called a topical anesthetic to numb the area where you will receive your injection.
- Your doctor will begin the procedure by giving you the first injection, then pausing to allow the anesthetic that is part of Restylane Refyne to continue to numb the area around your injection site. The anesthetic part of Restylane Refyne has been shown to significantly reduce the pain and discomfort that may occur with a dermal filler gel injection.
- Your doctor will continue the injection of Restylane Refyne until the area being treated shows the desired results.
- After the injection is completed, your doctor may gently massage the area that was treated to ensure that the dermal filler gel is distributed evenly and looks natural.

11. AFTER PROCEDURE INFORMATION

What should I expect following the procedure?

In the clinical study the most common side effects were temporary reactions at the treatment site such as tenderness, swelling, firmness, and lumps/bumps. These side effects generally lasted 1 to 2 weeks. See Section 8 for additional information on side effects seen in the clinical study.

Your doctor will also tell you what to expect following treatment. For the first 24 hours, you should avoid or minimize hard (strenuous) exercise. You should also avoid or minimize exposure to extensive sun or heat. Exposure to any of these may cause the area where you were treated to temporarily become red, swell and/or itch. If you experience any of these, an ice pack can be applied for relief.

12. ALTERNATIVE PROCEDURES

What other treatments are available to me?

There are other dermal filler gels in the United States that are available to you for treatment. Additionally, there are alternative treatments such as botulinum toxins, laser therapy and chemical peels for the treatment of lines and wrinkles. You can discuss these treatments with your doctor to determine which one is right for you.

13. WHEN TO CALL YOUR DOCTOR

When should I call my doctor?

You should call your doctor if you have any of the following side effects that last for more than 14 days:

- Bruising
- Swelling
- Pain
- Tenderness
- Redness
- Itching

These side effects typically go away within two weeks.

If you experience fever, redness that spreads to areas around the injection site, drainage, or increasing tenderness or pain that does not go away, you may be at risk for developing an infection. You should call your doctor so that you can be treated with antibiotics.

If you develop blisters or recurring skin sores, this may be cold sores. You should call your doctor so that you can be treated.

If you experience any of the following symptoms, you should call your doctor immediately:

- Unusual pain
- Vision changes
- A white appearance in the skin near the injection site

Any sign 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) during or shortly after the procedure (http://www.nlm.nih.gov/medlineplus/stroke.html).

14. ADDITIONAL INFORMATION

What if I experience a problem?

If you believe that you have experienced a serious problem related to Restylane Refyne you should call your doctor. Your questions about Restylane Refyne can be personally answered by contacting the Galderma Laboratories L.P. toll-free call center between 8:00 a.m. and 5:00 p.m. Central Daylight Time, Monday to through Friday.

1-855-425-8722

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