

# LABELING

## Restylane

**Caution:** Federal Law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

### Description

Restylane is a gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically crosslinked with BDDE, stabilized and suspended in physiologic buffer at pH = 7 and concentration of 20mg/ml.

### Indication

Restylane is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

### Contraindications

- Restylane is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Restylane contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- Restylane is contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.
- Restylane must not be implanted into blood vessels. Implantation of Restylane into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

### Warnings

Use of Restylane at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the inflammatory process has been controlled.

Hypersensitivity as an inflammatory reaction to Restylane has been observed with swelling, redness, tenderness, induration and rarely acneform papules at the injection site. Refer to the adverse events section for details.

Injection site reaction to Restylane has been observed consisting mainly of short-term inflammatory symptoms starting early after treatment and with less than 7 days duration. Refer to the clinical study section for details.

Localized superficial necrosis may occur after injection in the glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.

The safety or efficacy of Restylane for the treatment of lips has not been established in controlled clinical studies.

### Precautions

Restylane is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.

Based on US clinical studies patients should be limited to 1.5cc per treatment site. The safety of injecting greater amounts has not been established.

The safety or effectiveness of Restylane for the treatment of anatomic regions other than nasolabial folds has not been established in controlled clinical studies.

Long-term safety and effectiveness of Restylane beyond one year have not been investigated in clinical trials.

As with all transcutaneous procedures, Restylane implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.

The safety of Restylane for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.

The safety of Restylane in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied. Restylane should not be used in patients with known susceptibility to keloid formation or hypertrophic scarring.

Restylane should be used with caution in patients on immunosuppressive therapy.

Patients who are using substances that reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.

After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

Restylane is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe and notify Medicis Aesthetics, Inc. at 1-866-222-1480.

The patient should be informed that he or she should minimize exposure of the treated area to excessive sun and UV lamp exposure and extreme cold weather until any initial swelling and redness has resolved.

If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with Restylane there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if Restylane is administered before the skin has healed completely after such a procedure.

Restylane is supplied in a syringe ready for use. Never mix Restylane with other products prior to injection of the device.

#### Adverse Events

In a study of 138 patients at 6 centers, adverse events reported in Restylane patient diaries during 14 days after treatment are reported in the following table. Patients in the study received Restylane injections in one side of the face, and a bovine collagen dermal filler (Zyplast) in the other side of the face:

Table 1  
Maximum Intensity of Symptoms after Initial Treatment, Patient Diary

	Restylane side	Zyplast side	Restylane side				Zyplast side			
	Total reporting symptoms n (%)	Total reporting symptoms n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Bruising	72 (52.2)	67 (48.6)	63 (45.6)	32 (23.2)	35 (25.4)	5 (3.6)	68 (49.3)	43 (31.2)	23 (16.7)	0
Redness	117 (84.8)	117 (84.8)	17 (12.3)	56 (40.6)	54 (39.1)	7 (5.1)	17 (12.3)	72 (52.2)	37 (26.8)	0
Swelling	120 (87.0)	102 (73.9)	14 (10.1)	54 (39.1)	61 (44.2)	5 (3.6)	32 (23.2)	65 (47.1)	35 (25.4)	0
Pain	79 (57.2)	58 (42.0)	55	40	34	5	76	46	10	0

			(39.9)	(29.0)	(24.6)	(3.6)	(55.1)	(33.3)	(7.2)	(1
Tenderness	107 (77.5)	89 (64.5)	27 (19.6)	60 (43.5)	43 (31.2)	4 (2.9)	45 (32.6)	70 (50.7)	17 (12.3)	(1
Itching	42 (30.4)	33 (23.9)	91 (65.9)	31 (22.5)	11 (8.0)	0 (0.0)	101 (73.2)	27 (19.6)	6 (4.4)	(1
Other	34 (24.6)	33 (23.9)	93 (67.4)	14 (10.1)	15 (10.9)	5 (3.6)	94 (68.1)	20 (14.5)	10 (7.2)	(2

Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.

Table 2  
Duration of Adverse Events after Initial Treatment, Patient Diary

	Restylane side	Zyplast side	Restylane side				Zyplast side			
	Total reporting symptoms n	Total reporting symptoms n	Number of days				Number of days			
			1 n (%)	2-7 n (%)	8-13 n (%)	14- n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14- n (%)
Bruising	72 (52.2)	67 (48.6)	7 (5.1)	56 (40.6)	6 (4.4)	3 (2.2)	7 (5.1)	53 (38.4)	5 (3.6)	2 (1.4)
Redness	117 (84.8)	117 (84.8)	19 (13.8)	68 (49.3)	18 (13.0)	12 (8.7)	19 (13.8)	71 (51.4)	15 (10.9)	12 (8.7)
Swelling	120 (87.0)	102 (73.9)	16 (11.6)	84 (60.9)	16 (11.6)	4 (2.9)	14 (10.1)	70 (50.7)	16 (11.6)	2 (1.4)
Pain	79 (57.2)	58 (42.0)	29 (21.0)	48 (34.8)	2 (1.4)	0 (0.0)	31 (22.5)	25 (18.1)	1 (0.7)	1 (0.7)
Tenderness	107 (77.5)	89 (64.5)	21 (15.2)	78 (56.5)	6 (4.4)	2 (1.4)	27 (19.6)	54 (39.1)	6 (4.4)	2 (1.4)
Itching	42 (30.4)	33 (23.9)	11 (8.0)	25 (18.1)	6 (4.4)	0 (0.0)	8 (5.8)	22 (15.9)	3 (2.2)	0 (0.0)
Other	34 (24.6)	33 (23.9)	7 (5.1)	23 (16.7)	3 (2.2)	1 (0.7)	10 (7.2)	15 (10.9)	6 (4.4)	2 (1.4)

Table 3  
Other Adverse Events Reported in the Randomized Study from Physician Case Report Forms

Description of adverse event type (WHO preferred term)	N n = 138
INFLECTED INJURY	8
SINUSITIS	7
UPPER RESP TRACT INFECTION	6
ACNE	5
BACK PAIN	3
DEPRESSION	3
DEPRESSION AGGRAVATED	3
TOOTH DISORDER	4

BRONCHITIS	2
PNEUMONIA	2
DERMATITIS CONTACT	2
ALLERGIC REACTION*	2
ARTHRALGIA	2
OSTEOPOROSIS	2
HEADACHE	2
MIGRAINE	2
HERPES SIMPLEX	2
HYPERCHOLESTEROLEMIA	2
URINARY INCONTINENCE	2

\* One case of seasonal allergy, and one reaction to make-up in the peri-orbital area

In postmarket surveillance in other countries, presumptive bacterial infections, inflammatory adverse events, allergic adverse events, and necrosis have been reported. Reported treatments have included systemic steroids, systemic antibiotics, and intravenous administrations of medications. Additionally, inflammatory reaction to Restylane has been observed with swelling, redness, tenderness, induration and rarely acneform papules at the injection site with onset at one to several weeks after the initial treatment in previously unexposed individuals, and in less than 7 days following treatment in patients known to have been previously exposed. Average duration of this effect is 2 weeks. Medicis is conducting a post-approval study to determine the likelihood of hypersensitivity reactions for patients receiving Restylane injections.

Adverse reactions should be reported to Medicis Aesthetics Inc. 1-866-222-1480

#### Clinical Trial

The safety and effectiveness of RESTYLANE for the treatment of facial wrinkles and folds was evaluated in a randomized, controlled study. RESTYLANE was shown to be safe and effective when compared to an approved cross-linked collagen dermal implant, as to duration of the augmentation of nasolabial folds at 6 month follow-up after optimal cosmesis was achieved.

Randomized study	
Design	<p>1 to 1 randomized, prospective study at 6 US centers, which compared the safety and effectiveness of Restylane and Zyplast in a 'within-patient' control model of augmentation correction of bilateral nasal folds, using Restylane on the randomized nasal labial fold and the control treatment on the opposite nasal labial fold. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were unmasked</p> <p>Effectiveness was studied with 6 month follow-up. Safety was studied with 12 month follow-up.</p>
Endpoints	<p>Effectiveness</p> <p>Primary: The difference in effect of Restylane and Zyplast on the visual severity of the nasolabial folds, as assessed by an Evaluating Investigator at 6 months after 'baseline'.</p> <p>Secondary: Wrinkle severity rating scale (SRS) score assessed at other follow-up points by the evaluating investigator and by the subject.</p>

	<p>Global Aesthetic Improvement (GAI): Very much improved / much improved / improved / no change / worse, assessed at 2, 4, and 6 months by the evaluating investigator and by the subject.</p> <p>Number of treatment sessions to achieve optimal cosmesis.</p> <p>The primary evaluation parameter was the 5 - point SRS Score. A change in SRS = 1 was considered to be clinically significant during follow-up. Baseline was defined to begin at the follow-up demonstrating that optimal correction had been sustained for 2 weeks.</p> <p>Optimal correction was defined to be the best cosmetic result obtainable, as determined by the evaluating physician. A specific, objective score or goal for correction was not defined; 2 injectable implant sessions were expected.</p>
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## Outcomes

### Demographics

The study enrolled a population of predominately healthy, female, Caucasian non-smokers with history of prior facial aesthetic procedures and minimal sun exposure. There were few men or other racial / ethnic groups; few smokers or patients with extensive sun exposure. Medicis is conducting a post-approval study to determine the likelihood of keloid formation in patients with Fitzpatrick Scale skin types 5 and 6 receiving Restylane injections.

- Gender

Male: 9 (6.6%)  
 Female: 128 (93.4%)

- Ethnicity

Caucasian: 122 (89.0%)  
 Black: 2 (1.5%)  
 Asian: 2 (1.5%)  
 Hispanic: 11 (8.0%)

- Tobacco use

Non-smoking: 118 (86.1%)  
 Smokers: 19 (13.9%)

- Sun Exposure

None: 83 (60.6%)  
 Natural Sun: 52 (38.0%)  
 Artificial: 2 (1.5%)

## Effectiveness

### Primary

Based on the per patient evaluation, the SRS scores at 6 months by the evaluating investigator demonstrated that SRS for

Restylane was lower (better) than Control:	in 78 patients
Restylane was equal to Control:	in 46 patients
Restylane was higher (worse) than Control:	in 13 patients

For the entire cohort, however, the Mean of the SRS Score by evaluating investigator demonstrated that while there was essentially no difference between Restylane and Control treated cohort sides at pre-treatment (0.02 Units SRS) and baseline (0.01 Units SRS), for the cohort of 134 patients, there was a difference of 0.58 units of SRS at 6 months.

	N	Restylane	Control	Absolute Difference
Pre-treatment	138	3.29	3.31	0.02
Baseline	138	1.80	1.79	0.01
6 months	134	2.36	2.94	0.58

#### How supplied

RESTYLANE is supplied in a disposable glass syringe with a Luer-lok fitting. A gamma irradiation sterilized needle, 30 G x ½", is co-packed with each syringe of RESTYLANE.

A patient record label is a part of the syringe label (see picture C). Remove it by pulling the flap marked with three small arrows (see picture D). This label is to be attached to patient records to ensure traceability of the product. The contents of the syringe are sterile.

The volume in each syringe is as stated on the syringe label and on the carton.

#### Directions for Use

##### Assembly of needle to syringe

For safe use of RESTYLANE it is important that the needle is properly assembled. See pictures A and B.

A. Unscrew the tip cap of the syringe carefully.

B 1. Take a loose grip on the narrow part of the needle shield and mount the needle on the Luer-lok by screwing until you feel some counterpressure.

B 2. Take a new firm grip on the wider part of the needle shield. Press and turn it a further 90° (a quarter of a turn).

B 3. Pull off the needle shield.

#### Treatment Procedure

1. It is necessary to counsel the patient and discuss the appropriate indication, risks, benefits and expected responses to the RESTYLANE treatment. Advise the patient of the necessary precautions before commencing the procedure.
2. Assess the patient's need for pain management.
3. Clean the area to be treated with alcohol or another suitable antiseptic solution.
4. Before injecting, press the rod carefully until a small droplet is visible at the tip of the needle.
5. RESTYLANE is administered using a thin gauge needle (30G x ½"). The needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle or fold. The bevel of the needle should face upwards and the substance should be injected into the middle of the dermis. Tip: for mid-dermis placement the contour of the needle should be visible but not the color of it.

If RESTYLANE is injected too deep or intramuscularly, the duration of the effect will be shorter. If RESTYLANE is injected too superficially this may result in visible lumps and/or grayish discoloration.

6. Inject RESTYLANE applying even pressure on the plunger rod while slowly pulling the needle backwards. The wrinkle should be lifted and eliminated by the end of the injection. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
7. Only correct to 100% of the desired volume effect. Do not overcorrect. With cutaneous contour deformities the best results are obtained if the defect can be manually stretched to the point where it is eliminated. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique. Markedly indurated defects may be difficult to correct.
8. The injection technique with regard to the depth of injection and the administered quantity may vary. The linear threading technique, serial punctual injections or a combination of the two have been used with success.
9. When the injection is completed the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying superficial bone to obtain optimal results.
10. If so called "blanching" is observed, i.e. the overlying skin turns a whitish color, the injection should be stopped immediately and the area massaged until it returns to a normal color.
11. If the wrinkle needs further treatment, the same procedure should be repeated with several punctures of the skin until a satisfactory result is obtained. Additional treatment with RESTYLANE may be necessary to achieve the desired correction. With patients who have localized swelling the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient to a touch-up session after 1 - 2 weeks.
12. Typical usage for each treatment session is less than 2ml per treatment site.
13. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period.
14. Patients may have mild to moderate injection site reactions, which typically resolve in few days.
15. **Note!** The correct injection technique is crucial for the final result of the treatment.

**STERILE NEEDLE, 1 × 30 G × ½"**

- Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not resheat used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.

**Shelf life and storage**

RESTYLANE must be used prior to the expiration date printed on the package.

Store at a temperature of up to 25° C (77° F). Do not freeze and protect from sunlight. Refrigeration is not needed.

Do not resterilize RESTYLANE as this may damage or alter the product.

Do not use if the package is damaged. Immediately return the damaged product to Medicis Aesthetics, Inc.

Rx only

US Patent 5,827,937

Manufactured for

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\* RESTYLANE is a registered trademark of Medicis.

**Watson, Anthony**

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**From:** Ted Sullivan [t.sullivan@q-med.com]  
**Sent:** Friday, December 12, 2003 4:32 PM  
**To:** Watson, Anthony  
**Subject:** Re: Labeling Again

Q-Med concurs on the labeling sent with the message below.

Ted Sullivan  
Q-Med Scandinavia, Inc.

----- Original Message -----

**From:** Watson, Anthony  
**To:** 'Ted Sullivan'  
**Sent:** Friday, December 12, 2003 4:30 PM  
**Subject:** Labeling Again

Ted,

We are close! Here is the labeling. I have highlighted in yellow all changes. Your concurrence is appreciated.

<<Restylane IFU Modified 12-12-03.doc>>

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